10/622,817

1 = 7-18-2002

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File   5:Biosis Previews(R) 1969-2005/Mar W3
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Set     Items   Description
S1          2   P38 AND PARKIN
S2       1563   P38 AND BINDING
S3       2106   SB203580
S4       1957   SB203580 AND P38
S5         57   PARKIN AND BINDING
S6          3   AU='HAMPE CORNELIA'
S7        175   AU='BRICE ALEXIS'
S8         50   AU='PRADIER LAURANT' OR AU='PRADIER LAURENT'
S9         32   E4-E6
S10       157   AU='FOURNIER ALAIN'
S11       399   S6 OR S7 OR S8 OR S9 OR S10
S12         2   P38 AND S11
? t s1/7/1-2

 1/7/1
DIALOG(R)File   5:Biosis Previews(R)
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0014365745   BIOSIS NO.: 200300324041
The %%%p38%%% subunit of the aminoacyl-tRNA synthetase complex is a
  %%%Parkin%%% substrate: Linking protein biosynthesis and
  neurodegeneration.
AUTHOR: Corti Olga; Hampe Cornelia; Koutnikova Hana; Darios Frederic;
  Jacquier Sandrine; Prigent Annick; Robinson Jean-Charles; Pradier Laurent
  ; Ruberg Merle; Mirande Marc; Hirsch Etienne; Rooney Thomas; Fournier
  Alain; Brice Alexis (Reprint)
AUTHOR ADDRESS: INSERM U289, Hopital de la Salpetriere, 47 Boulevard de
  l'Hopital, Batiment Pharmacie, 75651, Paris Cedex 13, France**France
AUTHOR E-MAIL ADDRESS: brice@ccr.jussieu.fr
JOURNAL: Human Molecular Genetics  12 (12): p1427-1437 15 June, 2003 2003
MEDIUM: print
ISSN: 0964-6906 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Parkinson's disease (PD) is a severe neurological disorder,
  characterized by the progressive degeneration of the dopaminergic
  nigrostriatal pathway and the presence of Lewy bodies (LBs). The
  discovery of genes responsible for familial forms of the disease has
  provided insights into its pathogenesis. Mutations in the %%%parkin%%%
  gene, which encodes an E3 ubiquitin-protein ligase involved in the
  ubiquitylation and proteasomal degradation of specific protein
  substrates, have been found in nearly 50% of patients with
  autosomal-recessive early-onset parkinsonism. The abnormal accumulation
  of substrates due to loss of %%%Parkin%%% function may be the cause of
  neurodegeneration in %%%parkin%%%-related parkinsonism. Here, we
  demonstrate that %%%Parkin%%% interacts with, ubiquitylates and promotes
  the degradation of %%%p38%%%, a key structural component of the mammalian
  aminoacyl-tRNA synthetase complex. We found that the ubiquitylation of
  %%%p38%%% is abrogated by truncated variants of %%%Parkin%%% lacking
  essential functional domains, but not by the pathogenic Lys161Asn point
  mutant. Expression of %%%p38%%% in COS7 cells resulted in the formation
  of aggresome-like inclusions in which %%%Parkin%%% was systematically
  sequestered. In the human dopaminergic neuroblastoma-derived SH-SY5Y cell
  line, %%%Parkin%%% promoted the formation of ubiquitylated %%%p38%%%
  -positive inclusions. Moreover, the overexpression of %%%p38%%% in
  SH-SY5Y cells caused significant cell death against which %%%Parkin%%%
  provided protection. Analysis of %%%p38%%% expression in the human adult
  midbrain revealed strong immunoreactivity in normal dopaminergic neurons
  and the labeling of LBs in idiopathic PD. This suggests that %%%p38%%%
  plays a role in the pathogenesis of PD, opening the way for a detailed
  examination of its potential non-canonical role in neurodegeneration.

 1/7/2
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DIALOG(R)File 5:Biosis Previews(R)
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0014347322 BIOSIS NO.: 200300304811
%%%PARKIN%%% UBIQUITINATES AND PROMOTES THE DEGRADATION OF %%%P38%%%, A SCAFFOLD SUBUNIT OF THE AMINOACYL - tRNA SYNTHETASE COMPLEX.
AUTHOR: CORTI O (Reprint); Hampe C (Reprint); Koutnikova H; Darios F (Reprint); Periquet M (Reprint); Jacquier S (Reprint); Pradier L; Fournier A; Ruberg M (Reprint); Rooney T; Brice A (Reprint)
AUTHOR ADDRESS: INSERM U 289, Paris, France**France
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 484.6 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Parkinson's disease is a neurodegenerative disorder characterized by predominant loss of nigrostriatal dopaminergic neurons. Clues to its pathophysiology have been recently provided by the discovery of genes implicated in familial forms of the disease. Mutations in the %%%parkin%%% gene are a frequent cause of familial parkinsonism with autosomal recessive inheritance and early onset. %%%Parkin%%% is a ubiquitin protein ligase involved in the degradation of proteins via the ubiquitin-proteasome pathway. Loss of %%%Parkin%%% function, due to disease-related %%%Parkin%%% gene mutations, may lead to aberrant accumulation of potentially toxic substrates that could cause dopaminergic neuronal death.)We report the identification of a new %%%Parkin%%% substrate, %%%p38%%%, a structural component of the aminoacyl-tRNA synthetase complexes involved in protein biosynthesis. This protein was isolated as a potential %%%Parkin%%% partner in a yeast two-hybrid screen using %%%Parkin%%% as bait. Interaction between %%%Parkin%%% and %%%p38%%% was confirmed by co-immunoprecipitation from COS7 cells overexpressing both proteins. Furthermore, exogenous %%%p38%%% was shown to accumulate in perinuclear aggresomes recruiting %%%Parkin%%% , as well as endogenous Hsp70, ubiquitin and the 20S proteasome. In the neuroblastoma-derived cell line SH-SY5Y overexpression of %%%Parkin%%% led to significant ubiquitination of %%%p38%%% and promoted %%%p38%%% proteasomal degradation. These results open the way for a detailed examination of the potential dual function of %%%p38%%% in protein biosynthesis and in the pathogenesis of PD.

P38-t binding

? t s2/7/1550-1563

2/7/1550
DIALOG(R)File 5:Biosis Previews(R)
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0007152944 BIOSIS NO.: 199089070835
ISOLATION AND SEQUENCING OF NOP1 A YEAST GENE ENCODING A NUCLEOLAR PROTEIN HOMOLOGOUS TO A HUMAN AUTOIMMUNE ANTIGEN
AUTHOR: HENRIQUEZ R (Reprint); BLOBEL G; ARIS J P
AUTHOR ADDRESS: LAB CELL BIOL, HOWARD HUGHES MED INST, ROCKEFELLER UNIV, NEW YORK, NEW YORK 10021, USA**USA
JOURNAL: Journal of Biological Chemistry 265 (4): p2209-2215 1990
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have identified the gene for the yeast nucleolar protein %%%p38%%% and deduced the primary structure of %%%p38%%% from its sequence. We propose the name NOP1 (nucleolar protein 1) for this gene. NOP1 encodes a 327 amino acid protein of 34,470 daltons and is flanked by potential promoter and polyadenylation sequences. Blot analyses indicate that the mRNA transcribed from NOP1 is approximately 1.3 kilobases in size and that there is one NOP1 gene per haploid genome. The

amino-terminal sequence of %%%p38%%% is homologous with the 31 known amino-terminal residues of the autoimmune antigen fibrillarin, confirming the previously observed similarity between %%%p38%%% and this mammalian nucleolar protein. Consistent with this, %%%p38%%% crossreacts with serum from a patient with the autoimmune disease scleroderma. A putative nuclear localization signal can be identified in %%%p38%%%. Interestingly, a repetitive amino acid sequence motif begins near the amino terminus of %%%p38%%%. This motif is approximately 80 residues long, is rich in glycine and arginine, and shows striking sequence homology to mammalian nucleolins and certain nucleic acid %%%binding%%% proteins.

2/7/1551
DIALOG(R)File 5:Biosis Previews(R)

0007130131 BIOSIS NO.: 199089048022
A CIS DOWNSTREAM ELEMENT PARTICIPATES IN REGULATION OF IN-VITRO TRANSCRIPTION INITIATION FROM THE %%%P38%%% PROMOTER OF MINUTE VIRUS OF MICE
AUTHOR: KRAUSKOPF A (Reprint); RESNEKOV O; ALONI Y
AUTHOR ADDRESS: DEP MOL GENET VIROL, WEIZMANN INST SCI, REHOVOT 76100, ISRAEL**ISRAEL
JOURNAL: Journal of Virology 64 (1): p354-360 1990
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We report the use of a HeLa whole cell extract (WCE) runoff transcription system for the study of cis- and trans-acting elements, participating in the regulation of transcription initiation from the %%%P38%%% promoter of the parvovirus minute virus of mice (MVM). Our initial studies with HeLa WCE indicated that transcription from the %%%P38%%% promoter is very inefficient, compated with transcription from the P4 promoter. Supplementation of the HeLa WCE with WCE prepared from uninfected Ehrlich ascites cells enhanced transcription from the %%%P38%%% promoter twofold, indicating a role for a cellular factor in transcription from the %%%P38%%% promoter. Furthermore, supplementation with WCE prepared from MVM-infected Ehrlich ascites cells enhanced transcription from the %%%P38%%% promoter about sixfold, indicating a role for a virally encoded or induced factor. Analysis of runoffs produced by transcription of DNA templates digested with various restriction enzymes defined a downstream promoter element (DPE) necessary for efficient transcription initiation from the %%%P38%%% promoter. This element resides 282 to 647 base pairs 3' to the transcription initiation site, between the NarI site and the HindIII site (2287 to 2652, MVM numbering system). The virally encoded NS1 protein was shown by DNA precipitation to bind directly or indirectly through a cellular factor to the DPE. This interaction is suggested to be involved in the up regulation of the %%%P38%%% promoter of MVM. Finally, with a DNAse I protection assay performed on a fragment containing the DPE, we estimated the sequence involved in the %%%binding%%% of a factor present in uninfected and infected extracts. The correlation between the %%%binding%%% and transcription activation is discussed.

2/7/1552
DIALOG(R)File 5:Biosis Previews(R)

0006803107 BIOSIS NO.: 198988118222
SUBCELLULAR DISTRIBUTION OF 65000 CALMODULIN-%%%BINDING%%% PROTEIN P65 AND SYNAPTOPHYSIN %%%P38%%% IN ADRENAL MEDULLA
AUTHOR: FOURNIER S (Reprint); NOVAS M L; TRIFARO J-M
AUTHOR ADDRESS: SECRETORY PROCESS RES PROGRAM, DEP PHARMACOL, FAC HEALTH SCIENCES, UNIV OTTAWA, OTTAWA, ONTARIO, CANADA**CANADA
JOURNAL: Journal of Neurochemistry 53 (4): p1043-1049 1989
ISSN: 0022-3042
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Both neuronal and endocrine cells contain secretory vesicles that store and release neutrotransmitters and peptides. Neuronal cells release their secretory material from both small synaptic vesicles and large dense-core vesicles (LDCVs), whereas endocrine cells release secretory products from LDCVs. Neuronal small synaptic vesicles are known to express three integral membrane proteins: 65,000 calmodulin-%%%binding%%% protein (65-CMBP)(p65), synaptophysin (%%%p38%%%), and SV2. A controversial question surrounding these three proteins is whether they are present in LDCV membranes of endocrine and neuronal cells. Sucrose density centrifugation of adrenal medulla was performed to study and compare the subcellular distribution of two of these small synaptic vesicle proteins (65-CMBP and synaptophysin). Subsequent immunoblotting and 125I-Protein A bindign experiments performed on the fractions obtained from sucrose gradients showed that 65-CMBP was present in fractions corresponding to granule membranes and intact chromaffin granules. Similar immunoblotting and 125I-Protein A %%%binding%%% experiments with synaptophysin antibodies showed that this protein was also present in intact granules and granule membrane fractions. However, an additional membrane component, equilibrating near the upper portion of the sucrose gradient, also showed strong immunoreactivity with anti-synaptophysin and high 125I-Protein A %%%binding%%% activity. In addition, immunoblotting experiments on purified plasma and granule membranes demonstrated that 65-CMBP was a component of both membranes, whereas synaptophysin was only present in granule membranes. Thus, there appears to be a different subcellular localization between 65-CMBP and synaptophysin in the chromaffin cell.

2/7/1553
DIALOG(R)File 5:Biosis Previews(R)

0006603313 BIOSIS NO.: 198987051204
UPTAKE OF GABA BY RAT BRAIN SYNAPTIC VESICLES ISOLATED BY A NEW PROCEDURE
AUTHOR: HELL J W (Reprint); MAYCOX P R; STADLER H; JAHN R
AUTHOR ADDRESS: DEP NEUROCHEM, MAX-PLANCK-INST PSYCHIATRY, D-8033 MARTINSRIED**WEST GERMANY
JOURNAL: EMBO (European Molecular Biology Organization) Journal 7 (10): p 3023-3030 1988
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Uptake of GABA was demonstrated in rat brain synaptic vesicles which were prepared by a new and efficient procedure. The uptake activity co-purified with the synaptic vesicles during the isolation procedure. The purity of the vesicle fraction was rigorously examined by analysis of marker enzymes and marker proteins and also by immunogold electron microscopy using antibodies against %%%p38%%% (synaptophysin). Contamination by other cellular components was negligible, indicating that GABA uptake by the synaptic vesicle fraction is specific for synaptic vesicles and not due to the presence of other structures possessing GABA uptake or %%%binding%%% activities. GABA uptake was ATP dependent and similar to the uptake of glutamate, which was assayed for a comparison. BOth uptake activities were independent of sodium. They were inhibited by the uncoupler carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone, indicating that the energy for the uptake is provided by an electrochemical proton gradient. This gradient is generated by a proton ATPase of the vacuolar type as suggested by the effects of various ATPase inhibitors on neurotransmitter uptake and proton pumping. Competition experiments revealed that the transporters for GABA and glutamate are selective for the respective neurotransmitters.

2/7/1554
DIALOG(R)File 5:Biosis Previews(R)

0006599466 BIOSIS NO.: 198987047357
TWO PROTEINS CROSSLINKED TO RNA CONTAINING THE ADENOVIRUS L3 POLY ADENYLIC ACID SITE REQUIRE THE AAUAAA SEQUENCE FOR %%%BINDING%%%
AUTHOR: MOORE C L (Reprint); CHEN J; WHORISKEY J
AUTHOR ADDRESS: DEP MOL BIOL MICROBIOL, TUFTS UNIV SCH MED, BOSTON, MASS 02111, USA**USA
JOURNAL: EMBO (European Molecular Biology Organization) Journal 7 (10): p 3159-3170 1988
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The major proteins crosslinked by UV light to RNA containing the adenovirus-2 L3 poly(A) site are species of 155, 68 and 38 kd mol. wt (p155, p68 and %%%p38%%%). Mutation of AAUAAA to AAGAAA prevented cross-linking of the two larger proteins and destroyed the ability of the RNA to compete for %%%binding%%% of these proteins. However, association of p155 and p68 with precursor was unaffected by deletion of sequences downstream of the poly(A) site critical for in vitro polyadenylation. These two proteins are in the polyadenylation-specific, but not the nonspecific complexes detected by electrophoresis in nondenaturing gels. In addition, p155 and p68 are not found on RNA which has been processed. p155 bound a 15-nt oligomer containing AAUAAA, and thus does not require extended RNA sequence for interaction with RNA. Identified by immunoprecipitation with specific antibody, %%%p38%%% is the C protein of heterogeneous ribonucleoprotein particles (hnRNPs). While p155 has an Sm epitope, it is not associated with snRNPs containing trimethylated guanosine caps.

2/7/1555
DIALOG(R)File 5:Biosis Previews(R)

0006094112 BIOSIS NO.: 198885063003
ISOLATION OF A MAJOR HUMAN PLACENTAL SUBSTRATE FOR THE EPIDERMAL GROWTH FACTOR UROGASTRONE RECEPTOR KINASE IMMUNOLOGICAL CROSS-REACTIVITY WITH TRANSDUCIN AND SEQUENCE HOMOLOGY WITH LIPOCORTIN
AUTHOR: VALENTINE-BRAUN K A (Reprint); HOLLENBERG M D; FRASER E; NORTHUP J K
AUTHOR ADDRESS: DEP PHARMACOL AND THERAPEUTICS, FAC MED, UNIV CALGARY, 3330 HOSPITAL DRIVE NORTHWEST, CALGARY, ALBERTA, CAN T2N 4N1**CANADA
JOURNAL: Archives of Biochemistry and Biophysics 259 (2): p262-282 1987
ISSN: 0003-9861
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Using as a starting material either a detergent extract or a protein fraction eluted from membranes with ethylene glycol bis (.beta.-aminoethyl ether)-N,N'-tetraacetic acid, we have isolated from human placental membranes a major substrate for the epidermal growth factor (urogastrone) receptor kinase (EGF kinase). The substrate was isolated both in an intact form, having a molecular mass of approximately 38-kDa (%%%p38%%%), and in a 35-kDa form (p35) representing a proteolytic cleavage product of %%%p38%%%. Both %%%p38%%% and p35 cross-reacted with antibodies directed against bovine retinal transducin, but did not cross-react with antibodies directed against the 35-kDa .beta. subunit of human placental G-protein. Antisera directed against the placental EGF kinase substrate failed to react with either bovine or human placental src kinase substrate, p36. Conversely, antisera directed against p36 reacted only poorly with placental %%%p38%%% or p35. Although %%%p38%%% had a blocked amino terminus that precluded sequence analysis, p35 yielded an N-terminal sequence that was identical with residues 13-36 of human lipocortin. Our data clearly distinguish %%%p38%%% from the previously described intestinal calcium %%%binding%%% protein calpactin I or p36 that is also a tyrosine kinase substrate, and our work points to a close relationship (if not identify) between p35 and a 35-kDa EGF

receptor kinase substrate previously characterized in A431 cells. We conclude that %%%p38%%% and p35, which very likely represent human placental lipocortin, may share only limited epitope homology with transducin .alpha. subunit; however, the possibility that %%%p38%%%, along with intestinal p36 and with a family of related calcium %%%binding%%% protein, may, like transducin, play a role in receptor-mediated transmembrane signaling is discussed.

2/7/1556
DIALOG(R)File 5:Biosis Previews(R)

0006091599 BIOSIS NO.: 198885060490
CLONING AND SEQUENCE ANALYSIS OF COMPLEMENTARY DNA ENCODING %%%P38%%% A MAJOR SYNAPTIC VESICLE PROTEIN
AUTHOR: BUCKLEY K M (Reprint); FLOOR E; KELLY R B
AUTHOR ADDRESS: DEP BIOCHEM BIOPHYSICS, UNIV CALIF AT SAN FRANCISCO SCH MED, SAN FRANCISCO, CA 94143-0448, USA**USA
JOURNAL: Journal of Cell Biology 105 (6 PART 1): p2447-2456 1987
ISSN: 0021-9525
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have isolated from a lambda gt11 rat brain cDNA library cDNA clones encoding > 95% of the open reading frame and untranslated regions of the mRNA for %%%p38%%%, the most abundant of the integral membrane proteins of the synaptic vesicle. Phage containing cDNA that encoded vesicle proteins were identified by screening fusion proteins with a polyclonal serum to rat brain synaptic vesicles. To identify phage carrying %%%p38%%% sequences, fusion proteins were used to affinity purify monospecific antibodies from the original heterogeneous serum; antibodies from 38,000-D protein were then identified by Western blotting. Inserts carrying DNA-encoding %%%p38%%% sequences were subcloned into plasmid vectors and used to generate cDNA probes for Northern blot analysis. A major transcript of 2.4 kb was expressed specially in brain and endocrine tissue but not in liver, consistent with the tissue-specific expression of the protein detected by antibody techniques. Using three overlapping clones that encoded fusion proteins, we identified and sequenced .apprx. 85% of the cDNA. Two additional Eco RI fragments at the 5' end of the mRNA were obtained from a fourth clone identified by screeening a second lambda gt11 library with a 5' cDNA probe. The cDNA encoded an open reading frame of 298 amino acids with a 3' untranslated region of 1.4 kb. The protein shares no sequence homology with other Ca2+-%%%binding%%% proteins. The availability of a cDNA clone for an integral synaptic vesicle protein should facilitate studies of its function in transmitter release, its intracellular targeting, and regulation of synaptic vesicle biogenesis during development and regeneration of nerve terminals.

2/7/1557
DIALOG(R)File 5:Biosis Previews(R)

0006071201 BIOSIS NO.: 198885040092
A SYNAPTIC VESICLE PROTEIN WITH A NOVEL CYTOPLASMIC DOMAIN AND FOUR TRANSMEMBRANE REGIONS
AUTHOR: SUDHOF T C (Reprint); LOTTSPEICH F; GREENGARD P; MEHL E; JAHN R
AUTHOR ADDRESS: HOWARD HUGHES MED INST, DEP MOLECULAR GENETICS, UNIV TEXAS HEALTH SCI CENT, DALLAS, TEX 75235, USA**USA
JOURNAL: Science (Washington D C) 238 (4830): p1142-1144 1987
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Complementary DNA and genomic clones were isolated and sequenced corresponding to rat and human synaptophysin (%%%p38%%%), a major integral membrane protein of synaptic vesicles. The deduced amino acid

sequences indicate an evolutionarily highly conserved protein that spans the membrane four times. Both amino and carboxyl termini face the cytoplasm, with the latter containing ten copies of a tyrosine-rich pentapeptide repeat. The structure of synaptophysin suggests that the protein may function as a channel in the synaptic vesicle membrane, with the carboxyl terminus serving as a %%%binding%%% site for cellular factors.

2/7/1558
DIALOG(R)File 5:Biosis Previews(R)

0005059285 BIOSIS NO.: 198681023176
DEPHOSPHORYLATION OF CYTOPLASMIC NON-POLYSOMAL MESSENGER RIBONUCLEOPROTEINS FROM CRYPTOBIOTIC GASTRULAE OF ARTEMIA-SALINA
AUTHOR: VAN HOVE L (Reprint); THOEN C; COHEN P; SLEGERS H
AUTHOR ADDRESS: DEP BIOCHEM, UNIV INSTELLING ANTWERPEN, UNIVERSITEITSPLEIN 1, B-2610 WILRIJK, BELGIUM**BELGIUM
JOURNAL: Biochemical and Biophysical Research Communications 131 (3): p 1241-1250 1985
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Cytoplasmic non-polysomal mRNP from crytobiotic gastrulae of the brine shrimp Artemia salina do not contain endogeneous protein phosphatase activity. However, both non-polysomal mRNP and purified mRNP proteins, phosphorylated by mRNP associated protein kinase, can be dephosphorylated by protein phosphatases purified from A. salina cytosol and rabbit skeletal muscle. The 38 kDa and 23.5 kDa poly(A) %%%binding%%% proteins (%%%P38%%% and P23.5) and a 65 kDa protein are the major substrates of each protein phosphatase used. The reversible phosphorylation-dephosphorylation of mRNP may be involved in the regulation of mRNP metabolism, by altering the poly(A) %%%binding%%% capacities of the mRNP proteins.

2/7/1559
DIALOG(R)File 5:Biosis Previews(R)

0004755550 BIOSIS NO.: 198580064445
A 38000-DALTON MEMBRANE PROTEIN P-38 PRESENT IN SYNAPTIC VESICLES
AUTHOR: JAHN R (Reprint); SCHIEBLER W; OUIMET C; GREENGARD P
AUTHOR ADDRESS: LABORATORY MOLECULAR AND CELLULAR NEUROSCIENCE, ROCKEFELLER UNIVERSITY, 1230 YORK AVENUE, NEW YORK, NY 10021, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 82 (12): p4137-4141 1985
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A protein with an apparent molecular mass of 38,000 daltons designated %%%p38%%% was found in synaptic vesicles from rat brain. The subcellular distribution of %%%p38%%% and some of its properties were determined with the aid of polyclonal and monoclonal antibodies. The subcellular distribution of %%%p38%%% was similar to that of synapsin I, a synaptic-vesicle specific phosphoprotein. %%%p38%%% in the synaptic vesicle fraction purified by controlled-pore glass bead chromatography showed an enrichment of more than 20-fold over the crude homogenate. Immunostaining of sections through various brain regions revealed an intense labeling of most, and possibly all, nerve terminals. Only faint reactions in the region of the Golgi apparatus and no detectable labeling of axons and dendrites was observed. Two-dimensional electrophoresis revealed that %%%p38%%% has an acidic pI [isoelectric point]. Solubilization experiments, as well as phase separation experiments using Triton X-114, indicated that %%%p38%%% is an integral membrane protein. %%%Binding%%% of antibodies to intact synaptic vesicles, as well as

controlled proteolytic digestion of intact and detergent-treated vesicles, revealed that %%%p38%%% has a domain exposed on the cytoplasmic surface.

2/7/1560
DIALOG(R)File 5:Biosis Previews(R)

0004198458 BIOSIS NO.: 198477030369
MYCOPLASMA-HYORHINIS GDL SURFACE PROTEIN ANTIGEN P-120 DEFINED BY MONO CLONAL ANTIBODY
AUTHOR: WISE K S (Reprint); WATSON R K
AUTHOR ADDRESS: DEP MICROBIOL, SCH MED, UNIV MISSOURI-COLUMBIA, COLUMBIA, MO 65212, USA**USA
JOURNAL: Infection and Immunity 41 (3): p1332-1339 1983
ISSN: 0019-9567
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Four antigens of M. hyorhinis GDL were defined by murine monoclonal antibodies. Components of broth-grown mycoplasmas were separated under reducing conditions by sodium dodecyl sulfate-polyacrylamide gel electrophoresis; subsequent protein blots were stained with individual antibodies. Each antibody reacted with a distinct component with relative MW of 120,000, 73,000, 51,000 and 38,000, respectively (termed p120, p73, p51 and %%%p38%%%). Trypsin treatment of protein blots specifically abrogated %%%binding%%% of antibodies, suggesting that the epitopes recognized were associated with proteins. By using indirect immunofluorescence and immunoferritin techniques, mycoplasmas colonizing the surface of chronically infected BW5147 murine T lymphoblastoid cells were selectively stained with antibody to p120, indicating the localization of the corresponding epitope at the mycoplasma surface. Protein blots of mycoplasmas derived from BW5147 cell cultures were stained with antibody to p120, revealing a component identical to that observed with broth-grown organisms. These results establish the identity of a surface protein antigen of M. hyorhinis GDL expressed at the surface of organisms during their colonization of host cells.

2/7/1561
DIALOG(R)File 5:Biosis Previews(R)

0003996110 BIOSIS NO.: 198376087545
SUB CELLULAR DISTRIBUTION IN XENOPUS-LAEVIS OOCYTES OF A MICRO INJECTED POLY ADENYLIC-ACID %%%BINDING%%% PROTEIN FROM ARTEMIA-SALINA GASTRULAE
AUTHOR: DE HERDT E (Reprint); MARBAIX G; TENCER R; SLEGERS H
AUTHOR ADDRESS: DEP CELLBIOL, UNIV INSTELLING ANTWERPEN, UNIVERSITEITSPLEIN 1, B-2610 WILRIJK, BELGIUM**BELGIUM
JOURNAL: European Journal of Biochemistry 132 (3): p623-628 1983
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The poly(A)-%%%binding%%% protein %%%P38%%% of non-polysomal mRNP [messenger ribonucleoprotein] from A. salina gastrulae was labeled by reductive methylation and microinjected into the cytoplasm of X. laevis oocytes. The labeled protein has a half-life of approximately 20 h and accumulated in the nucleus of the oocyte. The kinetics of accumulation reached a plateau at about 15 h after microinjection. %%%P38%%% accumulates in the nucleus to a final concentration 3.15 times higher than that reached by free diffusion. %%%P38%%%, a cytoplasmic poly(A)-%%%binding%%% protein, might also play some role in the nucleus of the cell.

2/7/1562

DIALOG(R)File 5:Biosis Previews(R)

0003910026 BIOSIS NO.: 198376001461
PARTIAL PURIFICATION OF A RNA %%%BINDING%%% CYCLIC AMP INDEPENDENT PROTEIN KINASE FROM EMBRYONIC CHICKEN MUSCLE
AUTHOR: HUDSON A P (Reprint); BAG J; SELLS B H
AUTHOR ADDRESS: LAB MOLECULAR BIOL, FAC MED, MEMORIAL UNIV NEWFOUNDLAND, ST JOHN'S, NFLD, CANADA A1B 3V6**CANADA
JOURNAL: Canadian Journal of Biochemistry 60 (9): p890-896 1982
ISSN: 0008-4018
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A cAMP-independent protein kinase (%%%P38%%% kinase) from embryonic chicken muscle with ability to phosphorylate a 38,000 MW polypeptide and to bind to RNA was further characterized. An .apprx. 2000-fold purification of this enzyme was achieved by a combination of affinity and ion-exchange chromatography. Present studies indicate that this protein kinase can not phosphorylate the small subunit of rabbit reticulocyte initiation factor eIF-2 in the presence of its normal endogenous substrate, nor is it activated over a wide range of concentrations of double-stranded RNA. This %%%P38%%% kinase is distinct from hemin-regulated translational inhibitor of protein synthesis in rabbit reticulocytes and from the interferon-induced protein kinase identified in several systems.

2/7/1563
DIALOG(R)File 5:Biosis Previews(R)

0002188943 BIOSIS NO.: 197764037299
CHARACTERIZATION OF POLY PEPTIDES ASSOCIATED WITH MESSENGER RNA AND ITS POLY ADENYLATE SEGMENT IN EHRLICH ASCITES MESSENGER RIBO NUCLEO PROTEIN
AUTHOR: JEFFERY W R
JOURNAL: Journal of Biological Chemistry 252 (10): p3525-3532 1977
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Unspecified

ABSTRACT: Cytoplasmic messenger ribonucleoprotein (mRNP) was isolated from Ehrlich ascites tumor cells by oligo(dT)-cellulose chromatography and the proteins associated with mRNA and its poly(A) segment were characterized by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The most prominent polypeptides found in the mRNP fractions exhibited MW of 38,000 (%%%P38%%%), 40,000 (P40), 53,000 (P53), 56,000 (P56), 67,000 (P67), 71,000 (P71), 77,000 (P77), 81,000 (P81), 106,000 (P106), and 131,000 (P131). Experiments in which the %%%binding%%% of mRNP with oligo(dT)-cellulose was modified by saturation of oligo(dT) sequences with poly(A) or the poly(A) segments in mRNP with poly(U) prior to chromatography suggested that P56, P67, P71, P81, P106 and P131 were associated with mRNA in mRNP, while %%%P38%%%, P40 and P53 were non-mRNP components. Chromatography of ribosomes, in which the mRNP had been removed by mild RNase treatment, showed that %%%P38%%% and P40 were of ribosomal origin. RNase treatment of total RNP liberated a 13 S poly(A).cntdot.protein complex which could be isolated by oligo(dT)-cellulose chromatography. The poly(A).cntdot.protein complex contained polypeptides P56, P67, P71 and P81. The former 3 polypeptides were also present in the salt wash of total RNP and formed complexes with poly(A) in vitro. The poly(A) segment apparently serves as a %%%binding%%% site for 4 of the polypeptide species characteristic of mRNP isolated by oligo(dT)-cellulose chromatography.
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2/7/1200
DIALOG(R)File 5:Biosis Previews(R)

0012679308 BIOSIS NO.: 200000397621
Prolactin-induced cell proliferation in PC12 cells depends on JNK but not ERK activation
AUTHOR: Cheng Yu; Zhizhin Igor; Perlman Robert L; Mangoura Dimitra (Reprint)
AUTHOR ADDRESS: Dept. of Pediatrics, Kennedy Center, MC 5058, WCH C-576, Chicago, IL, 60637-1470, USA**USA
JOURNAL: Journal of Biological Chemistry 275 (30): p23326-23332 July 28, 2000 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effects of pituitary and extrapituitary prolactin include cellular proliferation and differentiation. PC12 cells was used as a model to delineate respective signaling of prolactin. Prolactin acted as a mitogen for undifferentiated PC12 cells, as measured by significant increases in bromodeoxyuridine incorporation and in cell numbers, with an efficacy equal to epidermal growth factor. Both the long and short form of the prolactin receptor was expressed, yet only the long isoform was tyrosine-phosphorylated upon agonist %%%binding%%%. Functional prolactin receptor signaling was further demonstrated in the activation of JAK2 and phosphorylation activation of the transcription factors Stat1, -3, and -5a. Surprisingly, prolactin stimulated a sustained activation of Raf-B, without activation of the MAP kinases ERK1 or -2. Instead, in solid phase kinase assays using a glutathione S-transferase-c-Jun fusion protein (amino acids 1-79) as the substrate, a significant activation of the mitogen-activated protein Janus kinase (c-Jun N-terminal kinase; JNK) was observed. The prolactin-induced activation of JNK was prolonged and accompanied by a significant increase in c-Jun mRNA abundance and c-Jun protein synthesis. Moreover, analysis of bromodeoxyuridine incorporation at the single cell level revealed that epidermal growth factor-dependent incorporation was inhibited by PD98059 and independent of SB203580, whereas prolactin-induced incorporation was ERK and mitogen-activated protein kinase %%%p38%%% independent but was abolished with JNK inhibition by 30 muM SB203580. Our studies suggest that prolactin may have a role in the growth of PC12 cells, where it stimulates concurrent mitogenic and differentiation-promoting signaling pathways.

2/7/1201
DIALOG(R)File 5:Biosis Previews(R)

0012670771 BIOSIS NO.: 200000389084
Phosphorylation of eIF-4E on Ser 209 in response to mitogenic and inflammatory stimuli is faithfully detected by specific antibodies
AUTHOR: Tschopp C (Reprint); Knauf U (Reprint); Brauchle M (Reprint); Zurini M (Reprint); Ramage P (Reprint); Glueck D (Reprint); New L; Han J (Reprint); Gram H (Reprint)
AUTHOR ADDRESS: NOVARTIS Pharma AG, CH-4002, Basel, Switzerland** Switzerland
JOURNAL: Molecular Cell Biology Research Communications 3 (4): p205-211 April, 2000 2000
MEDIUM: print
ISSN: 1522-4724
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Phosphorylation of Ser 209 is thought to modulate the activity of the cap-%%%binding%%% factor eIF-4E which is a crucial component in the initiation complex for cap-dependent translation of mRNA. We report here the full reconstitution of the %%%p38%%% Map kinase cascade leading to phosphorylation of eIF-4E in vitro and the generation of antibodies specific for phospho-serine 209 in eIF-4E. These antibodies were used to probe the phosphorylation of eIF-4E in mammalian cells stimulated with

mitogens and pro-inflammatory cytokines. Treatment of human dermal fibroblasts with FCS led to a transient hyperphosphorylation, followed by hypophosphorylation and return to normal state phosphorylation at 16 h after the initial stimulation. By using a potent small molecular weight inhibitor of Mnk1, the upstream kinase for eIF-4E, we observed a rapid dephosphorylation of eIF-4E within 45 min after addition of the inhibitor, suggesting a high turnover of phosphate on eIF-4E mediated by Mnk1 and a yet unidentified phosphatase.

2/7/1202
DIALOG(R)File 5:Biosis Previews(R)

0012669094 BIOSIS NO.: 200000387407
Molecular mechanisms of apoptosis induced by an immunomodulating peptide on human monocytes
AUTHOR: Oses-Prieto Juan A; Lopez-Moratalla Natalia; Santiago Esteban; Jaffrezou Jean P; Lopez-Zabalza Maria J (Reprint)
AUTHOR ADDRESS: Departamento de Bioquimica, Universidad de Navarra, C/Irunlarrea 1, 31008, Pamplona, Navarra, Spain**Spain
JOURNAL: Archives of Biochemistry and Biophysics 379 (2): p353-362 July 15, 2000 2000
MEDIUM: print
ISSN: 0003-9861
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A short immunomodulating peptide (Pa) containing a defined structural motif present in a number of extracellular matrix proteins and autoantigens was found to stimulate human monocytes. Pa-induced apoptosis of isolated monocytes, as indicated by inter-nucleosomal DNA cleavage, increased annexin V %%%binding%%% capacity and cleavage of caspase substrates, such as poly(ADP)ribosylypolymerase. In addition, Bcl-2 protein levels were downregulated during Pa-induced cell death. Nuclear extracts of monocytes incubated with Pa showed higher neutral, Ca2+-dependent DNase activity than those obtained from nontreated monocytes. Caspase inhibitors prevented Pa-induced apoptosis, Bcl-2 depletion, and DNase activation. Treatment of monocytes with Pa activated c-Jun N-terminal kinases and %%%p38%%% kinase, in an acidic sphingomyelinase- and caspase-dependent fashion. Pa-induced apoptosis was blocked by selective inhibitors of %%%p38%%% kinase (SB203580) and acidic sphingomyelinase (SR33557). These results indicate that JNK and %%%p38%%% kinase stimulation as well as monocyte apoptosis induced by Pa could depend, at least in part, on early activation of acidic sphingomyelinase.

2/7/1203
DIALOG(R)File 5:Biosis Previews(R)

0012668936 BIOSIS NO.: 200000387249
Nitric oxide induces heme oxygenase-1 via mitogen-activated protein kinases ERK and %%%p38%%%
AUTHOR: Chen Kai; Maines Mahin D (Reprint)
AUTHOR ADDRESS: Department of Biochemistry and Biophysics, University of Rochester School of Medicine, 601 Elmwood Ave., Rochester, NY, 14642, USA **USA
JOURNAL: Cellular and Molecular Biology (Noisy-Le-Grand) 46 (3): p609-617 May, 2000 2000
MEDIUM: print
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Heme oxygenase-1 (HO), the heat shock/stress cognate of the heat shock protein 32 (HSP32) family of proteins, is postulated to be a component of cellular defense mechanisms against oxidative stress-mediated injury. Nitric oxide (NO) is among the extensive array of stimuli that induce HO-1. The cellular signaling mechanisms that regulate

the induction of HO-1 by NO are not understood. In the present study, we have demonstrated that exposure of HeLa cells to the NO donor, sodium nitroprusside (SNP), results in concentration and time-dependent increase in HO-1 mRNA and activation of MAPKs: ERK (ERK1 and ERK2) and %%%p38%%% pathways, but not SAPK/JNK pathway. Pre-treatment of the cells with PD98059, a selective ERK pathway inhibitor, and SB203580, a %%%p38%%% MAPK inhibitor, blocked the induction of HO-1 by the NO donor in a dose-dependent manner. In addition, an increase in HO-1 mRNA level that was detected as early as 2 hrs.following SNP treatment preceded c-jun and c-fos induction. These transcription factors are downstream of SAPK/JNK pathway, and their increased expression was detected at 3hr.and 6hr.after SNP treatment. Similarly, AP-1 DNA %%%binding%%% activity was not increased when measured 6 hrs. after SNP treatment. ERK and %%%p38%%% inhibitors also suppressed induction of HO-1 by SNAP and GSNO. The increase in HO-1 mRNA was inhibited by actinomycin D and cycloheximide, but not by NAC, and was not mimicked by the lipophilic cGMP analogue, 8-bromo-cGMP, suggesting that NO-mediated induction required de novo RNA and protein synthesis and was unrelated to cGMP and redox signaling. Collectively, the findings suggest that MAP kinase ERK and %%%p38%%% pathways are involved in the NO-mediated induction of HO-1 and that SAPK/JNK pathway and increased DNA %%%binding%%% of AP-1 transcription factor are not involved in HO-1 gene activation by NO. A plausible mechanism by which the NO donors cause HO-1 induction may involve HO-1 gene regulation by its substrate, heme.

2/7/1204
DIALOG(R)File 5:Biosis Previews(R)

0012668645 BIOSIS NO.: 200000386958
Regulation of redox glutathione levels and gene transcription in lung inflammation: Therapeutic approaches
AUTHOR: Rahman Irfan (Reprint); MacNee William
AUTHOR ADDRESS: ELEGI Colt Research Laboratories, Medical School, University of Edinburgh, Teviot Place, Wilkie Building, Edinburgh, EH8 9AG, UK**UK
JOURNAL: Free Radical Biology and Medicine 28 (9): p1405-1420 May 1, 2000
2000
MEDIUM: print
ISSN: 0891-5849
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glutathione (L-gamma-glutamyl-L-cysteinylglycine, GSH), is a vital intra- and extracellular protective antioxidant. Glutathione is synthesized from its constituent amino acids by the sequential action of gamma-glutamylcysteine synthetase (gamma-GCS) and GSH synthetase. The rate-limiting enzyme in GSH synthesis is gamma-GCS. Gamma-GCS expression is modulated by oxidants, phenolic antioxidants, and inflammatory and anti-inflammatory agents in various mammalian cells. The intracellular GSH redox homeostasis is strictly regulated to govern cell metabolism and protect cells against oxidative stress. Growing evidence has suggested that cellular oxidative processes have a fundamental role in inflammation through the activation of stress kinases (JNK, MAPK, %%%p38%%%) and redox-sensitive transcription factors such as NF-kappaB and AP-1, which differentially regulate the genes for proinflammatory mediators and protective antioxidant genes such as gamma-GCS, Mn-SOD, and heme oxygenase-1. The critical balance between the induction of proinflammatory mediators and antioxidant genes and the regulation of the levels of GSH in response to oxidative stress at the site of inflammation is not known. Knowledge of the mechanisms of redox GSH regulation and gene transcription in inflammation could lead to the development of novel therapies based on the pharmacological manipulation of the production of this important antioxidant in inflammation and injury. This FORUM article features the role of GSH levels in the regulation of transcription factors, whose activation and DNA %%%binding%%% leads to proinflammatory and antioxidant gene transcription. The potential role of thiol antioxidants as a therapeutic approach in inflammatory lung diseases is also discussed.

2/7/1205
DIALOG(R)File 5:Biosis Previews(R)

0012666805 BIOSIS NO.: 200000385118
Cardiac ankyrin repeat protein is a novel marker of cardiac hypertrophy: Role of M-CAT element within the promoter
AUTHOR: Aihara Yasushi; Kurabayashi Masahiko (Reprint); Saito Yuichiro; Ohyama Yoshio; Tanaka Toru; Takeda Shin-ichi; Tomaru Kouichi; Sekiguchi Ken-ichi; Arai Masashi; Nakamura Tetsuya; Nagai Ryozo
AUTHOR ADDRESS: Second Department of Internal Medicine, Gunma University School of Medicine, 3-39-15, Showa-machi, Maebashi, Gunma, 371-8511, Japan**Japan
JOURNAL: Hypertension (Baltimore) 36 (1): p48-53 July, 2000 2000
MEDIUM: print
ISSN: 0194-911X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CARP, a cardiac doxorubicin (adriamycin)-responsive protein, has been identified as a nuclear protein whose expression is downregulated in response to doxorubicin. In the present study, we tested the hypothesis that CARP serves as a reliable genetic marker of cardiac hypertrophy in vivo and in vitro. CARP expression was markedly increased in 3 distinct models of cardiac hypertrophy in rats: constriction of abdominal aorta, spontaneously hypertensive rats, and Dahl salt-sensitive rats. In addition, we found that CARP mRNA levels correlate very strongly with the brain natriuretic peptide mRNA levels in Dahl rats. Transient transfection assays into primary cultures of neonatal rat cardiac myocytes indicate that transcription from the CARP and brain natriuretic peptide promoters is stimulated by overexpression of %%%p38%%% and Rac1, components of the stress-activated mitogen-activated protein kinase pathways. Mutation analysis and electrophoretic mobility shift assays indicated that the M-CAT element can serve as a %%%binding%%% site for nuclear factors, and this element is important for the induction of CARP promoter activity by %%%p38%%% and Rac1. Thus, our data suggest that M-CAT element is responsible for the regulation of the CARP gene in response to the activation of stress-responsive mitogen-activated protein kinase pathways. Moreover, given that activation of these pathways is associated with cardiac hypertrophy, we propose that CARP represents a novel genetic marker of cardiac hypertrophy.

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DIALOG(R)File 5:Biosis Previews(R)

0012666717 BIOSIS NO.: 200000385030
Nitric oxide reduces vascular smooth muscle cell elastase activity through cGMP-mediated suppression of ERK phosphorylation and AML1B nuclear partitioning
AUTHOR: Mitani Yoshihide; Zaidi Syed H E; Dufourcq Pascale; Thompson Karen; Rabinovitch Marlene (Reprint)
AUTHOR ADDRESS: Division of Cardiovascular Research, The Hospital for Sick Children, 555 University Avenue, Toronto, M5G 1X8, Canada**Canada
JOURNAL: FASEB Journal 14 (5): p805-814 April, 2000 2000
MEDIUM: print
ISSN: 0892-6638
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Nitric oxide (NO) reduces the severity of pulmonary vascular disease in rats as do elastase inhibitors. We therefore hypothesized that NO inhibits elastase by suppressing mitogen-activated protein kinases that trans-activate AML1B, a transcription factor for elastase. We used cultured pulmonary artery smooth muscle cells in which serum-treated elastin (STE) induces a > threefold increase in elastase activity as

evaluated by solubilization of (3H)-elastin. NO donors (SNAP and DETA NONO-ate) inhibited elastase in a dose-dependent manner as did a cGMP mimetic (8-pCPT-cGMP). SNAP inhibition of elastase was reversed by coadministration of a cGMP-PKG inhibitor (Rp-8-pCPT-cGMP). The STE-induced increase in phospho-ERK was suppressed by NO donors and the cGMP mimetic, and reversed by cGMP-PKG inhibitor, as was expression of AML1B and DNA %%%binding%%% in nuclear extracts. A concomitant increase in %%%p38%%% phosphorylation was also inhibited by SNAP, but whereas MEK inhibitor (PD98059) suppressed elastase and AML1B-DNA %%%binding%%%, a %%%p38%%% inhibitor (SB202190) did not. Our study uniquely links NO with inhibition of elastase-dependent matrix remodeling in vascular disease by suggesting a cGMP-PKG-related mechanism suppressing ERK-mediated partitioning of AML1B in nuclear extracts.

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DIALOG(R)File 5:Biosis Previews(R)

0012657778 BIOSIS NO.: 200000376091
Activation of %%%p38%%% mitogen-activated protein kinase is required for tumor necrosis factor-alpha-supported proliferation of leukemia and lymphoma cell lines
AUTHOR: Liu Richard Y (Reprint); Fan Chun; Liu Guoqing; Olashaw Nancy E; Zuckerman Kenneth S
AUTHOR ADDRESS: Division of Medical Oncology and Hematology, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL, 33612, USA**USA
JOURNAL: Journal of Biological Chemistry 275 (28): p21086-21093 July 14, 2000 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To elucidate mechanisms of tumor necrosis factor alpha (TNF-alpha)-induced proliferation of a number of human leukemia and lymphoma cell lines, we examined the role of %%%p38%%% mitogen-activated protein kinase (MAPK) in TNF-alpha signaling in Mo7e and Hut-78 cells. TNF-alpha-dependent %%%p38%%% MAPK activation was detected in both Mo7e and Hut-78 cells and was blocked by the %%%p38%%% MAPK inhibitor, SB203580. Ablation of %%%p38%%% MAPK activity by SB203580 abrogated TNF-alpha-induced Mo7e cell proliferation and TNF-alpha-dependent autocrine growth of Hut-78. As we have shown previously that activation of the nuclear factor kappaB (NF-kappaB) is also required for TNF-alpha-induced Mo7e cell proliferation, the involvement of %%%p38%%% MAPK in NF-kappaB activation was assessed. SB203580 did not affect TNF-alpha-signaled nuclear translocation and DNA-%%%binding%%% activity of NF-kappaB, and inhibition of NF-kappaB function did not affect TNF-alpha-induced %%%p38%%% MAPK activation, indicating that these events are not dependent on each other. However, SB203580 depressed the expression of NK-kappaB-dependent genes, as monitored by a kappaB-driven reporter gene. Our findings demonstrate that activation of both %%%p38%%% MAPK and NF-kappaB plays a critical role in TNF-alpha-mediated survival and proliferation of human leukemia and lymphoma cells, and %%%p38%%% MAPK acts at least in part by facilitating the transcriptional activation function of NF-kappaB.

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DIALOG(R)File 5:Biosis Previews(R)

0012655629 BIOSIS NO.: 200000373942
Vanadium-induced kappaB-dependent transcription depends upon peroxide-induced activation of the %%%p38%%% mitogen-activated protein kinase
AUTHOR: Jaspers Ilona (Reprint); Samet James M; Erzurum Serpil; Reed William
AUTHOR ADDRESS: Center for Environmental Medicine and Lung Biology, University of North Carolina at Chapel Hill, 104 Mason Farm Rd., Chapel

Hill, NC, 27599-7310, USA**USA
JOURNAL: American Journal of Respiratory Cell and Molecular Biology 23 (1): p95-102 July, 2000 2000
MEDIUM: print
ISSN: 1044-1549
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Activation of nuclear factor (NF)-kappaB and subsequent proinflammatory gene expression in human airway epithelial cells can be evoked by oxidative stress. In this study we examined signal transduction pathways activated by vanadyl sulfate (VIV)-induced oxidative stress in normal human bronchial epithelial cells. Both nuclear translocation of NF-kappaB and enhanced kappaB-dependent transcription induced by VIV were inhibited by overexpression of catalase, but not Cu,Zn superoxide dismutase (Cu,Zn-SOD), indicating that peroxides rather than superoxides initiated signaling. Catalase selectively blocked the response to VIV because it inhibited neither NF-kappaB translocation nor kappaB-dependent transcription evoked by the proin-flammatory cytokine tumor necrosis factor (TNF)-alpha. The VIV-induced kappaB-dependent transcription was dependent upon activation of the %%%p38%%% mitogen-activated protein kinase because overexpression of dominant-negative mutants of the %%%p38%%% MAPK pathway inhibited VIV-induced kappaB-dependent transcription. This inhibition was not due to suppression of NF-kappaB nuclear translocation because NF-kappaB DNA %%%binding%%% was unaffected by the inhibition of %%%p38%%% activity. Overexpression of catalase, but not Cu,Zn-SOD, inhibited %%%p38%%% activation, indicating that peroxides activated %%%p38%%%. Catalase failed to block VIV-induced increases in phosphotyrosine levels, suggesting that the catalase-sensitive signaling components were independent of VIV-induced tyrosine phosphorylation. The data demonstrate that VIV-induced oxidative stress activates at least two distinct pathways, NF-kappaB nuclear translocation and %%%p38%%% -dependent transactivation of NF-kappaB, both of which are required to fully activate kappaB-dependent transcription. Moreover, VIV-induced oxidative stress activated these pathways in bronchial epithelial cells by upstream signaling cascades that were distinct at some level from those used by the proinflammatory cytokine TNF-alpha.

2/7/1209
DIALOG(R)File 5:Biosis Previews(R)

0012641917 BIOSIS NO.: 200000360230
Microtubule-interfering agents stimulate the transcription of cyclooxygenase-2: Evidence for involvement of ERK1/2 and %%%p38%%% mitogen-activated protein kinase pathways
AUTHOR: Subbaramaiah Kotha (Reprint); Hart Janice C; Norton Larry; Dannenberg Andrew J
AUTHOR ADDRESS: Div. of Gastroenterology and Hepatology, New York Presbyterian Hospital-Cornell, 1300 York Ave., Rm. F-203, New York, NY, 10021, USA**USA
JOURNAL: Journal of Biological Chemistry 275 (20): p14838-14845 May 19, 2000 2000
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We investigated whether microtubule-interfering agents (MIAs: taxol, colchicine, nocodazole, vinblastine, vincristine, 17-beta-estradiol, 2-methoxyestradiol) altered cyclooxygenase-2 (COX-2) expression in human mammary epithelial cells. MIAs enhanced prostaglandin E2 synthesis and increased levels of COX-2 protein and mRNA. Nuclear run-off assays revealed increased rates of COX-2 transcription after treatment with MIAs. Calphostin C, an inhibitor of protein kinase C, blocked the induction of COX-2 by MIAs. The stimulation of COX-2 promoter activity by MIAs was inhibited by overexpressing dominant negative forms of Rho and Raf-1. MIAs stimulated ERK, JNK, and %%%p38%%%

mitogen-activated protein kinases (MAPK); pharmacological inhibitors of MAPK kinase and %%%p38%%% MAPK blocked the induction of COX-2 by MIAs. Overexpressing dominant negative forms of ERK1 or %%%p38%%% MAPK inhibited MIA-mediated activation of the COX-2 promoter. MIAs stimulated the %%%binding%%% of the activator protein-1 transcription factor complex to the cyclic AMP response element in the COX-2 promoter. A dominant negative form of c-Jun inhibited the activation of the COX-2 promoter by MIAs. Additionally, cytochalasin D, an agent that inhibits actin polymerization, stimulated COX-2 transcription by the same signaling pathway as MIAs. Thus, microtubule- or actin-interfering agents stimulated MAPK signaling and activator protein-1 activity. This led, in turn, to induction of COX-2 gene expression via the cyclic AMP response element site in the COX-2 promoter.

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DIALOG(R)File 5:Biosis Previews(R)

0012637840 BIOSIS NO.: 200000356153
Inhibition of %%%p38%%% MAP kinase as a therapeutic strategy
AUTHOR: Lee John C (Reprint); Kumar Sanjay; Griswold Don E; Underwood David C; Votta Bartholomew J; Adams Jerry L
AUTHOR ADDRESS: SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA, 19406, USA**USA
JOURNAL: Immunopharmacology 47 (2-3): p185-201 May, 2000 2000
MEDIUM: print
ISSN: 0162-3109
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Since the discovery of %%%p38%%% MAP kinase in 1994, our understanding of its biology has progressed dramatically. The key advances include (1) identification of %%%p38%%% MAP kinase homologs and protein kinases that act upstream and downstream from %%%p38%%% MAP kinase, (2) identification of interesting and potentially important substrates, (3) elucidation of the role of %%%p38%%% MAP kinase in cellular processes and (4) the establishment of the mechanism by which the pyridinylimidazole %%%p38%%% MAP kinase inhibitors inhibit enzyme activity. It is now known that there are four members of the %%%p38%%% MAP kinase family. They differ in their tissue distribution, regulation of kinase activation and subsequent phosphorylation of downstream substrates. They also differ in terms of their sensitivities toward the %%%p38%%% MAP kinase inhibitors. The best-studied isoform is %%%p38%%% alpha, whose activation has been observed in many hematopoietic and non-hematopoietic cell types upon treatment with appropriate stimuli. The pyridinylimidazole compounds, exemplified by SB 203580, were originally prepared as inflammatory cytokine synthesis inhibitors that subsequently were found to be selective inhibitors of %%%p38%%% MAP kinase. SB 203580 inhibits the catalytic activity of %%%p38%%% MAP kinase by competitive %%%binding%%% in the ATP pocket. X-ray crystallographic studies of the target enzyme complexed with inhibitor reinforce the observations made from site-directed mutagenesis studies, thereby providing a molecular basis for understanding the kinase selectivity of these inhibitors. The %%%p38%%% MAP kinase inhibitors are efficacious in several disease models, including inflammation, arthritis and other joint diseases, septic shock, and myocardial injury. In all cases, %%%p38%%% activation in key cell types correlated with disease initiation and progression. Treatment with %%%p38%%% MAP kinase inhibitors attenuated both %%%p38%%% activation and disease severity. Structurally diverse %%%p38%%% MAP kinase inhibitors have been tested extensively in preclinical studies.

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DIALOG(R)File 5:Biosis Previews(R)

0011587220 BIOSIS NO.: 199800381467
Anti-ischaemic action of transforming growth factor beta-1 in the rat

SB 203580 + p38

isolated heart is abolished by the %%%p38%%% MAPK inhibitor %%%SB203580%%%
AUTHOR: Mocanu M M (Reprint); Baxter G F; Yellon D M
AUTHOR ADDRESS: Victor Babes Inst., Bucharest, Romania**Romania
JOURNAL: British Journal of Pharmacology 123 (PROC. SUPPL.): p333P March, 1998 1998
MEDIUM: print
CONFERENCE/MEETING: Meeting of the British Pharmacological Society held jointly with Dutch Pharmacological Society, The Belgian Society for Fundamental and Clinical Physiology and Pharmacology Harrogate, England, UK December 10-12, 1997; 19971210
SPONSOR: Belgian Society for Fundamental and Clinical Physiology and Pharmacology
British Pharmacological Society
Dutch Pharmacological Society
ISSN: 0007-1188
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

4/7/1901
DIALOG(R)File 5:Biosis Previews(R)

0011563666 BIOSIS NO.: 199800357913
Hypertonicity regulates the function of human neutrophils by modulating chemoattractant receptor signaling and activating mitogen-activated protein kinase %%%p38%%%
AUTHOR: Junger Wolfgang G (Reprint); Hoyt David B; Davis Richard E; Herdon-Remelius Crystal; Namiki Sachiko; Junger Heidi; Loomis William; Altman Amnon
AUTHOR ADDRESS: Dep. Surg., Div. Trauma, Trauma Res. Lab. 8236, Univ. Calif. San Diego Med. Cent., 200 West Arbor Drive, San Diego, CA 92103-8236, USA**USA
JOURNAL: Journal of Clinical Investigation 101 (12): p2768-2779 June 15, 1998 1998
MEDIUM: print
ISSN: 0021-9738
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Excessive neutrophil activation causes posttraumatic complications, which may be reduced with hypertonic saline (HS) resuscitation. We tested if this is because of modulated neutrophil function by HS. Clinically relevant hypertonicity (10-25 mM) suppressed degranulation and superoxide formation in response to fMLP and blocked the activation of the mitogen activated protein kinases (MAPK) ERK1/2 and %%%p38%%%, but did not affect Ca2+ mobilization. HS did not suppress oxidative burst in response to phorbol myristate acetate (PMA). This indicates that HS suppresses neutrophil function by intercepting signal pathways upstream of or apart from PKC. HS activated %%%p38%%% by itself and enhanced degranulation in response to PKC activation. This enhancement was reduced by inhibition of %%%p38%%% with %%%SB203580%%%, suggesting that %%%p38%%% up-regulation participates in HS-induced enhancements of degranulation. HS had similar effects on the degranulation of cells that were previously stimulated with fMLP, but had no effect on its own, suggesting that HS enhancement of degranulation requires another signal. We conclude that depending on other stimuli, HS can suppress neutrophil activation by intercepting multiple receptor signals or augment degranulation by enhancing %%%p38%%% signaling. In patients HS resuscitation may reduce posttraumatic complications by preventing neutrophil activation via chemotactic factors released during reperfusion.

4/7/1902
DIALOG(R)File 5:Biosis Previews(R)

0011551201 BIOSIS NO.: 199800345448
Leptomycin B-sensitive nuclear export of MAPKAP kinase 2 is regulated by phosphorylation
AUTHOR: Engel Katrin; Kotlyarov Alexey; Gaestel Matthias (Reprint)
AUTHOR ADDRESS: Martin Luther Univ. Halle Wittenberg, Innovationskolleg Zellspezialisierung, Hoher Weg 8, 06120 Halle, Germany**Germany
JOURNAL: EMBO (European Molecular Biology Organization) Journal 17 (12): p 3363-3371 June 15, 1998 1998
MEDIUM: print
ISSN: 0261-4189
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To study the intracellular localization of MAPKAP kinase 2 (MK2), which carries a putative bipartite nuclear localization signal (NLS), we constructed a green fluorescent protein-MAPKAP kinase 2 fusion protein (GFP-MK2). In transfected cells, this protein is located predominantly in the nucleus; unexpectedly, upon stress, it rapidly translocates to the cytoplasm. This translocation can be blocked by the %%%p38%%% MAP kinase inhibitor %%%SB203580%%%, indicating its regulation by phosphorylation. Molecular mimicry of MK2 phosphorylation at T317 in GFP-MK2 led to a mutant which is located almost exclusively in the cytoplasm of the cell, whereas the mutant T317A shows no stress-induced redistribution. Since leptomycin B, which inhibits the interaction of exportin 1 with the Rev-type leucine-rich nuclear export signal (NES), blocks stress-dependent translocation of GFPMK2, it is supposed that phosphorylation-induced export of the protein causes the translocation. We have identified the region responsible for nuclear export in MK2 which is partially overlapping with and C-terminal to the autoinhibitory motif. This region contains a cluster of hydrophobic amino acids in the characteristic spacing of a leucine-rich Rev-type NES which is necessary to direct GFP-MK2 to the cytoplasm. However, unlike the Rev-type NES, this region alone is not sufficient for nuclear export. The data obtained indicate that MK2 contains a constitutively active NLS and a stress-regulated signal for nuclear export.

0011549774 BIOSIS NO.: 199800344021
Induction of Ets-1 in endothelial cells during reendothelialization after denuding injury
AUTHOR: Tanaka Katsuhiro (Reprint); Oda Nobuyuki; Iwasaka Chika; Abe Mayumi ; Sato Yasufumi (Reprint)
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JOURNAL: Journal of Cellular Physiology 176 (2): p235-244 Aug., 1998 1998
MEDIUM: print
ISSN: 0021-9541
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Ets-1, a transcription factor, is induced in endothelial cells (ECs) during angiogenesis. Here, we investigated the expression of Ets-1 during reendothelialization. When a confluent monolayer of human umbilical vein endothelial cell line, ECV304, was denuded, ECV304 at the wound edge expressed Ets-1. An immunohistochemical analysis revealed that Ets-1 accumulated in migrating cells at the wound edge and returned to basal level when reendothelialization was accomplished. This induction of Ets-1 could be reproduced in in vivo denudation of rat aortic endothelium by a balloon catheter. The induction of Ets-1 in ECs after denudation was regulated transcriptionally, and humeral factors released from injured ECs might not be responsible. Mitogen-activated protein kinase (MAPK) activities were investigated to explore the mechanism of this induction. Although extracellular signal-regulated protein kinase 1/2 (ERK1/2), c-jun N-terminal kinase 1 (jNK1), and %%%p38%%% were activated after denudation, the activation of ERK1 and %%%p38%%% was more rapid and

prominent. PD98059, a specific MAPK/ERK kinase (MEK) 1 inhibitor, did not affect the induction of ets-1 mRNA, whereas %%%SB203580%%%, a specific %%%p38%%% inhibitor, almost completely abrogated its induction. These results indicate that Ets-1 is induced in ECs after denudation through activation of %%%p38%%%. This induction of Ets-1 may be relevant for reendothelialization by regulating the expression of certain genes.

4/7/1904
DIALOG(R)File 5:Biosis Previews(R)

0011548704 BIOSIS NO.: 199800342951
%%%p38%%% Mitogen-activated protein kinase is a critical component of the redox-sensitive signaling pathways activated by angiotensin II: Role in vascular smooth muscle cell hypertrophy
AUTHOR: Ushio-Fukai Masuko (Reprint); Alexander R Wayne; Akers Marjorie; Griendling Kathy K
AUTHOR ADDRESS: Div. Cardiol., Emory Univ. Sch. Med., 1639 Pierce Dr., Room 319, Atlanta, GA 30322, USA**USA
JOURNAL: Journal of Biological Chemistry 273 (24): p15022-15029 June 12, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Angiotensin II induces an oxidant stress-dependent hypertrophy in cultured vascular smooth muscle cells. To investigate the growth-related molecular targets of H2O2, we examined the redox sensitivity of agonist-stimulated activation of the mitogen-activated protein kinase (MAPK) family. We show here that angiotensin II elicits a rapid increase in intracellular H2O2 and a rapid and robust phosphorylation of both p42/44MAPK (16-fold) and p38MAPK (15-fold). However, exogenous H2O2 activates only p38MAPK (14-fold), and diphenylene iodonium, an NADH/NADPH oxidase inhibitor, attenuates angiotensin II-stimulated phosphorylation of p38MAPK, but not p42/44MAPK. Furthermore, in cells stably transfected with human catalase, angiotensin II-induced intracellular H2O2 generation is almost completely blocked, resulting in inhibition of phosphorylation of p38MAPK, but not p42/44MAPK, and a subsequent partial decrease in angiotensin II-induced hypertrophy. Specific inhibition of either the p38MAPK pathway with %%%SB203580%%% (4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)5-(4-pyridyl)1H-imidazole) or the p42/44MAPK pathway with PD98059 (2-(2'-amino-3'-methoxyphenyl)oxanaphthalen-4-one) also partially, but significantly, attenuates angiotensin II-induced hypertrophy; however, simultaneous blockade of both pathways has an additive inhibitory effect, indicating that the hypertrophic response to angiotensin II requires parallel, independent activation of both MAPK pathways. These results provide the first evidence that p38MAPK is a critical component of the oxidant stress (H2O2)-sensitive signaling pathways activated by angiotensin II in vascular smooth muscle cells and indicate that it plays a crucial role in vascular hypertrophy.

4/7/1905
DIALOG(R)File 5:Biosis Previews(R)

0011520962 BIOSIS NO.: 199800315209
Activation of mitogen-activated protein kinases (%%%p38%%%-MAPKs, SAPKs/JNKs and ERKs) by the G-protein-coupled receptor agonist phenylephrine in the perfused rat heart
AUTHOR: Lazou Antigone; Sugden Peter H (Reprint); Clerk Angela
AUTHOR ADDRESS: NHLI Div., Imperial Coll. Sch. Med., Royal Brompton Campus, Doverhouse St., London SW3 6LY, UK**UK
JOURNAL: Biochemical Journal 332 (2): p459-465 June 1, 1998 1998
MEDIUM: print
ISSN: 0264-6021
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We investigated the ability of phenylephrine (PE), an alpha-adrenergic agonist and promoter of hypertrophic growth in the ventricular myocyte, to activate the three best-characterized mitogen-activated protein kinase (MAPK) subfamilies, namely %%%p38%%% -MAPKs, SAPKs/JNKs (i.e. stress-activated protein kinases/c-Jun N-terminal kinases) and ERKs (extracellularly responsive kinases), in perfused contracting rat hearts. Perfusion of hearts with 100 muM PE caused a rapid (maximal at 10 min) 12-fold activation of two %%%p38%%% -MAPK isoforms, as measured by subsequent phosphorylation of a %%%p38%%% -MAPK substrate, recombinant MAPK-activated protein kinase 2 (MAPKAPK2). This activation coincided with phosphorylation of %%%p38%%%-MAPK. Endogenous MAPKAPK2 was activated 4-5-fold in these perfusions and this was inhibited completely by the %%%p38%%%-MAPK inhibitor, %%%SB203580%%% (10 muM). Activation of %%%p38%%%-MAPK and MAPKAPK2 was also detected in non-contracting hearts perfused with PE, indicating that the effects were not dependent on the positive inotropic/chronotropic properties of the agonist. Although SAPKs/JNKs were also rapidly activated, the activation (2-3-fold) was less than that of %%%p38%%%-MAPK. The ERKs were activated by perfusion with PE and the activation was at least 50% of that seen with 1 muM PMA, the most powerful activator of the ERKs yet identified in cardiac myocytes. These results indicate that, in addition to the ERKs, two MAPK subfamilies, whose activation is more usually associated with cellular stresses, are activated by the Gq/11-protein-coupled receptor (Gq/11PCR) agonist, PE, in whole hearts. These data indicate that Gq/111PCR agonists activate multiple MAPK signalling pathways in the heart, all of which may contribute to the overall response (e.g. the development of the hypertrophic phenotype).

0011512357 BIOSIS NO.: 199800306604
Induction of cytokine-induced neutrophil chemoattractant in response to various stresses in rat C6 glioma cells
AUTHOR: Uehara Takashi; Baba Itsuko; Nomura Yasuyuki (Reprint)
AUTHOR ADDRESS: Dep. Pharmacol., Fac. Pharm. Sci., Hokkaido Univ., Sapporo 060, Japan**Japan
JOURNAL: Brain Research 790 (1-2): p284-292 April 20, 1998 1998
MEDIUM: print
ISSN: 0006-8993
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of stress on the production of cytokine-induced neutrophil chemoattractant (CINC) was examined in rat C6 glioma cells. We studied the production of CINC, an interleukin-8 (IL-8) family protein, with bacterial endotoxin, H2O2, and tumor necrosis factor-alpha (TNF-alpha). Each stress induced CINC mRNA in a concentration-dependent manner. Since stress activates the protein kinases regulating nuclear transcription factors, we examined the effects of protein kinase inhibitors and the over-expression of dominant-negative Ras on CINC mRNA expression. Neither over-expression of dominant-negative Ras nor pretreatment with PD98059 (MEK-1 inhibitor), %%%SB203580%%% (p38MAPK inhibitor), or GF109203X (protein kinase C (PKC) inhibitor) altered stress-induced CINC mRNA expression. This suggests that the Ras-MAPK, p38MAPK, and PKC pathways are not involved in CINC mRNA expression in glial cells. On the other hand, pretreatment with herbimycin A, a potent tyrosine kinase inhibitor, or Ro31-8220, a non-selective serine/threonine kinase inhibitor, suppressed stress-induced CINC mRNA expression. This indicates that stress-induced CINC mRNA expression is mediated by herbimycin A-, or Ro31-8220-sensitive kinases in glial cells. Since stress activates NF-kappaB and NF-IL6, we examined that the effect of herbimycin A, which suppresses CINC mRNA expression, on NF-kappaB and NF-IL6 activation. Herbimycin A suppressed NF-kappaB but not NF-IL6. These results suggest that in rat glial cells, the factors that induce

CINC mRNA expression are mediated by herbimycin A-sensitive NF-kappaB activation, but not through the PKC, Ras-MAPK or %%%p38%%% MAPK pathways.

4/7/1907
DIALOG(R)File 5:Biosis Previews(R)

0011502327 BIOSIS NO.: 199800296574
Analysis of the role of Hsp25 phosphorylation reveals the importance of the oligomerization state of this small heat shock protein in its protective function against TNFalpha- and hydrogen peroxide-induced cell death
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AUTHOR ADDRESS: Lab. Stress Cell., CNRS-UMR-5534, Centre Genet. Mol., Univ. Claude Bernard Lyon-I, 43, Bd du 11 Novembre 1918, 79722 Villeurbanne Cedex, France**France
JOURNAL: Journal of Cellular Biochemistry 69 (4): p436-452 June 15, 1998 1998
MEDIUM: print
ISSN: 0730-2312
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The role of murine Hsp25 phosphorylation in the protection mediated by this protein against TNFalpha- or H2O2-mediated cytotoxicity was investigated in L929 cell lines expressing wild type (wt-) or nonphosphorylatable (mt-) Hsp25. We show that mt-Hsp25, in which the phosphorylation sites, serines 15 and 86, were replaced by alanines, is still efficient in decreasing intracellular reactive oxygen species levels and in raising glutathione cellular content, leading the protective activity of mt-Hsp25 against oxidative stress to be identical to that of wt-Hsp25. To independently investigate the role of Hsp25 phosphorylation, we blocked TNFalpha-induced phosphorylation of wt-Hsp25 using %%%SB203580%%%, a specific inhibitor of the %%%P38%%% MAP kinase. This treatment did not abolish the protective activity of Hsp25 against TNFalpha. The pattern of Hsp25 oligomerization was also analyzed, showing mt-Hsp25 to constitutively display large native sizes, as does wt-Hsp25 after TNFalpha treatment in the presence of %%%SB203580%%%. Our results, therefore, are consistent with the possibility that the hyperaggregated form of Hsp25 is responsible for the protective activity against oxidative stress and that the phosphorylation of serines 15 and/or 86 by interfering with this structural reorganization, may lead to the inactivation of Hsp25 protective activity.

4/7/1908
DIALOG(R)File 5:Biosis Previews(R)

0011480816 BIOSIS NO.: 199800275063
Inhibitors of %%%p38%%% mitogen-activated protein kinase promote neuronal survival in vitro
AUTHOR: Horstmann Sonja; Kahle Philipp J; Borasio Gian Domenico (Reprint)
AUTHOR ADDRESS: Dep Neurol., Univ. Munich, Klinikum Grosshadern, Marchioninistr. 15, D-81377 Muenchen, Germany**Germany
JOURNAL: Journal of Neuroscience Research 52 (4): p483-490 May 15, 1998 1998
MEDIUM: print
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mammalian mitogen-activated protein kinases include the extracellular signal-regulated protein kinase, the c-Jun amino-terminal kinase, and the %%%p38%%% subgroups. Sustained activation of Jun kinase and %%%p38%%% have been shown to precede apoptosis of PC12 pheochromocytoma cells induced by withdrawal of trophic factors. To investigate the possible role of %%%p38%%% in neuronal apoptosis, we

tested the effect of two selective %%%p38%%% inhibitors, the pyridinyl imidazole compounds %%%SB203580%%% and SB202190, on different populations of chick embryonic neurons in vitro. Both substances promoted the in vitro survival of sensory, sympathetic, ciliary and motor neurons in a dose-dependent fashion. When assayed in nerve growth factor-stimulated PC12 cells, %%%SB203580%%% pretreatment inhibited the activation of both ribosomal S6 kinases-1 and -2 with the same IC50 (approximately 30 muM) that inhibited apoptosis in primary neurons. Thus, %%%p38%%% inhibitor-sensitive pathways may be involved in apoptosis of neurotrophic factor-deprived primary neurons, and in activation of ribosomal S6 kinases.

4/7/1909
DIALOG(R)File 5:Biosis Previews(R)

0011477908 BIOSIS NO.: 199800272155
T lymphocyte activation signals for interleukin-2 production involve activation of MKK6-%%%p38%%% and MKK7-SAPK/JNK signaling pathways sensitive to cyclosporin A
AUTHOR: Matsuda Satoshi; Moriguchi Tetsuo; Koyasu Shigeo (Reprint); Nishida Eisuke
AUTHOR ADDRESS: Dep. Immunol., Keio Univ. Sch. Med., Shinanomachi, Shinjuku-ku, Tokyo 160, Japan**Japan
JOURNAL: Journal of Biological Chemistry 273 (20): p12378-12382 May 15, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%p38%%%/CSBP, a subgroup member of mitogen-activated protein kinase (MAPK) superfamily molecules, is known to be activated by proinflammatory cytokines and environmental stresses. We report here that %%%p38%%% is specifically activated by signals that lead to interleukin-2 (IL-2) production in T lymphocytes. A %%%p38%%% activator MKK6 was also markedly activated by the same stimulation. Pretreatment of cells with %%%SB203580%%%, a specific inhibitor of %%%p38%%%, as well as expression of a dominant-negative mutant of MKK6, suppressed the transcriptional activation of the IL-2 promoter. We also demonstrated that MKK7, a recently described MAPK kinase family member, plays a major role in the activation of stress-activated protein kinase (SAPK)/c-Jun NH2-terminal kinase (JNK) in T lymphocytes. Moreover, a dominant-negative mutant of MKK7 abrogated the transcriptional activation of the distal nuclear factor of activated T cells response element in the IL-2 promoter. Cyclosporin A, a potent immunosuppressant, inhibited activation of both %%%p38%%% and SAPK/JNK pathways but not the MAPK/extracellular signal-regulated kinase (ERK) pathway. Our results indicate that both MKK6 to %%%p38%%% and MKK7 to SAPK/JNK signaling pathways are activated in a cyclosporin A-sensitive manner and contribute to IL-2 gene expression in T lymphocytes.

4/7/1910
DIALOG(R)File 5:Biosis Previews(R)

0011475812 BIOSIS NO.: 199800270059
Pervanadate inhibits mitogen-activated protein kinase kinase-1 in a p38MAPK-dependent manner
AUTHOR: Daum Gunter (Reprint); Kalmes Andreas; Levkau Bodo; Wang Yunxia; Davies Mark G; Clowes Alexander W
AUTHOR ADDRESS: Dep. Surgery, 1959 N.E. Pacific St., Box 356410, Univ. Washington, Seattle, WA 98195-6410, USA**USA
JOURNAL: FEBS Letters 427 (2): p271-274 May 8, 1998 1998
MEDIUM: print
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: In baboon smooth muscle cells (SMCs), pervanadate has a biphasic dose-dependent effect on MEK-1 activity. After a 30 min incubation period, low concentrations (1-10 muM) activate, while higher doses (30-100 muM) fail to stimulate MEK-1. One possibility is that higher doses of pervanadate induce an additional signaling pathway that inhibits MEK-1. Three lines of investigations provide support for the conclusion that this inhibitory effect is mediated by p38MAPK. First, pervanadate induces p38MAPK activity at concentrations that fail to activate MEK-1. Second, pervanadate-stimulated p38MAPK activity is maximal after a 10 min incubation, at a time, when MEK-1 activity disappears. Third, addition of the specific p38MAPK inhibitor %%%SB203580%%% preserves MEK-1 activation by 100 muM pervanadate. The inhibitory effect of p38MAPK is probably not due to a phosphorylation of MEK-1 although we can not rule out that other p38MAPK isoforms such as SAPK3 and SAPK4 may be involved, and may directly phosphorylate and inhibit MEK-1.

4/7/1911
DIALOG(R)File 5:Biosis Previews(R)

0011472662 BIOSIS NO.: 199800266909
The role of %%%p38%%% MAP kinase in TGF-beta1-induced signal transduction in human neutrophils
AUTHOR: Hannigan Michael (Reprint); Zhan Lijun; Ai Youxi; Huang Chi-Kuang
AUTHOR ADDRESS: Dep. Pathol., Univ. Conn. Health Cent., 263 Farmington Ave., Farmington, CT 06030-3105, USA**USA
JOURNAL: Biochemical and Biophysical Research Communications 246 (1): p 55-58 May 8, 1998 1998
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Transforming growth factor-beta1 (TGF-beta1) is the strongest chemoattractant yet described for human neutrophils. It activates neither phospholipase C nor phospholipase D. It does not induce rises in intracellular calcium, degranulation, or superoxide production. The signaling pathways utilized by TGF-beta1 are largely unknown. This report demonstrates that TGF-beta1 activates %%%p38%%% MAP kinase. The kinase inhibitor %%%SB203580%%% blocks the chemotactic responses as well as actin polymerization induced by TGF-beta1. Potential cellular targets of the %%%p38%%% MAP kinase pathway which could mediate these function are discussed.

4/7/1912
DIALOG(R)File 5:Biosis Previews(R)

0011461125 BIOSIS NO.: 199800255372
The %%%p38%%%-MAPK inhibitor, %%%SB203580%%%, inhibits cardiac stress-activated protein kinases/c-Jun N-terminal kinases (SAPKs/JNKs)
AUTHOR: Clerk Angela; Sugden Peter H (Reprint)
AUTHOR ADDRESS: NHLI Div., Imperial coll. Med., Dovehouse St., London SW3 6LY, UK**UK
JOURNAL: FEBS Letters 426 (1): p93-96 April 10, 1998 1998
MEDIUM: print
ISSN: 0014-5793
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%SB203580%%% is a recognised inhibitor of %%%p38%%%-MAPKs. Here, we investigated the effects of %%%SB203580%%% on cardiac SAPKs/JNKs. The IC50 for inhibition of %%%p38%%%-MAPK stimulation of MAPKAPK2 was approximately 0.07 muM, whereas that for total SAPK/JNK activity was 3-10 muM. %%%SB203580%%% did not inhibit immunoprecipitated

JNK1 isoforms. Three peaks of SAPK/JNK activity were separated by anion exchange chromatography, eluting in the isocratic wash (44 kDa), and at 0.08 M (46 and 52 kDa) and 0.15 M NaCl (54 kDa). %%%SB203580%%% (10 muM) completely inhibited the 0.15 M NaCl activity and partially inhibited the 0.08 M NaCl activity. Since JNK1 antibodies immunoprecipitate the 46 kDa activity, this indicates that %%%SB203580%%% selectively inhibits 52 and 54 kDa SAPKs/JNKs.

4/7/1913
DIALOG(R)File 5:Biosis Previews(R)

0011459424 BIOSIS NO.: 199800253671
Early activation of c-Jun N-terminal kinase and %%%p38%%% kinase regulate cell survival in response to tumor necrosis factor alpha
AUTHOR: Roulston Anne (Reprint); Reinhard Christoph; Amiri Payman; Williams Lewis T
AUTHOR ADDRESS: Chiron Corp., 4560 Horton St., M-338, Emeryville, CA 94608, USA**USA
JOURNAL: Journal of Biological Chemistry 273 (17): p10232-10239 April 24, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Fas ligand and tumor necrosis factor alpha (TNF) bind to members of the TNF receptor superfamily. Stimulation by Fas ligand results in apoptosis, whereas TNF induces multiple effects including proliferation, differentiation, and apoptosis. Activation of the c-Jun N-terminal kinase (JNK) and %%%p38%%% kinase pathways is common to Fas and TNF signaling; however, their role in apoptosis is controversial. Fas receptor cross-linking induces apoptosis in the absence of actinomycin D and activates JNK in a caspase-dependent manner. In contrast, TNF requires actinomycin D for apoptosis and activates JNK and %%%p38%%% kinase with biphasic kinetics. The first phase is transient, precedes apoptosis, and is caspase-independent, whereas the second phase is coincident with apoptosis and is caspase-dependent. Inhibition of early TNF-induced JNK and %%%p38%%% kinases using MKK4/MKK6 mutants or the %%%p38%%% inhibitor %%%SB203580%%% increases TNF-induced apoptosis, whereas expression of wild type MKK4/MKK6 enhances survival. In contrast, the Mek inhibitor PD098059 has no effect on survival. These results demonstrate that early activation of %%%p38%%% kinase (but not Mek) are necessary to protect cells from TNF-mediated cytotoxicity. Thus, early stress kinase activation initiated by TNF plays a key role in regulating apoptosis.

4/7/1914
DIALOG(R)File 5:Biosis Previews(R)

0011432227 BIOSIS NO.: 199800226474
Conditional expression of mitogen-activated protein kinase phosphatase-1, MKP-1, is cytoprotective against UV-induced apoptosis
AUTHOR: Franklin Christopher C; Srikanth Sampathkumar; Kraft Andrew S (Reprint)
AUTHOR ADDRESS: Dep. Med., Div. Med. Oncol., Univ. Colorado Health Sci. Center, Denver, CO 80262, USA**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 95 (6): p3014-3019 March 17, 1998 1998
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: UV irradiation induces apoptosis in U937 human leukemic cells that is accompanied by the activation of both the stress-activated protein kinase (SAPK) and %%%p38%%% mitogen-activated protein kinase

(MAPK) signal transduction pathways. The MAPK phosphatase, MKP-1, is capable of inactivating both SAPK and %%%p38%%% MAPK in vivo. To determine whether MKP-1-mediated inhibition of SAPK and/or %%%p38%%% MAPK activity provided cytoprotection against UV-induced apoptosis, a U937 cell line conditionally expressing MKP-1 from the human metallothionein IIa promoter was established. Conditional expression of MKP-1 was found to abolish UV-induced SAPK and %%%p38%%% MAPK activity, and inhibit UV-induced apoptosis as judged by both morphological criteria and DNA fragmentation. MKP-1 was also found to inhibit other biochemical events associated with apoptosis, including activation of caspase-3 and the proteolytic cleavage of the caspase-3 substrate, poly(ADP ribose) polymerase. These findings demonstrate that MKP-1 acts at a site upstream of caspase activation within the apoptotic program. The cytoprotective properties of MKP-1 do not appear to be mediated by its ability to inhibit %%%p38%%% MAPK because the %%%p38%%% MAPK specific inhibitor %%%SB203580%%% had no effect on UV-induced apoptosis in U937 cells. Furthermore, by titrating the level of MKP-1 expression it was found that MKP-1 inhibited UV-induced SAPK activity, DNA fragmentation, and caspase-3 activation in a similar dose-dependent manner. The dualspecificity phosphatase, PAC1, which does not inhibit UV-induced activation of SAPK, did not provide a similar cytoprotection against UV-induced apoptosis. These results are consistent with a model whereby MKP-1 provides cytoprotection against UV-induced apoptosis by inhibiting UV-induced SAPK activity.

0011431832 BIOSIS NO.: 199800226079
Stimulation of "stress-regulated" mitogen-activated protein kinases (stress-activated protein kinases/c-Jun N-terminal kinases and %%%p38%%% -mitogen-activated protein kinases) in perfused rat hearts by oxidative and other stresses
AUTHOR: Clerk Angela; Fuller Stephen J; Michael Ashour; Sugden Peter H (Reprint)
AUTHOR ADDRESS: NHLI Div., Imperial Coll. Sch. Med., Dovehouse St., London SW3 6LY, UK**UK
JOURNAL: Journal of Biological Chemistry 273 (13): p7228-7234 March 27, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: "Stress-regulated" mitogen-activated protein kinases (SR-MAPKs) comprise the stress-activated protein kinases (SAPKs)/c-Jun N-terminal kinases (JNKs) and the %%%p38%%%-MAPKs. In the perfused heart, ischemia/reperfusion activates SR-MAPKs. Although the agent(s) directly responsible is unclear, reactive oxygen species are generated during ischemia/reperfusion. We have assessed the ability of oxidative stress (as exemplified by H2O2) to activate SR-MAPKs in the perfused heart and compared it with the effect of ischemia/reperfusion. H2O2 activated both SAPKs/JNKs and %%%p38%%%-MAPK. Maximal activation by H2O2 in both cases was observed at 0.5 mm. Whereas activation of %%%p38%%%-MAPK by H2O2, was comparable to that of ischemia and ischemia/reperfusion, activation of the SAPKs/JNKs was less than that of ischemia/reperfusion. As with ischemia/reperfusion, there was minimal activation of the ERK MAPK subfamily by H2O2. MAPK-activated protein kinase 2 (MAPKAPK2), a downstream substrate of %%%p38%%%-MAPKs, was activated by H2O2 to a similar extent as with ischemia or ischemia/reperfusion. In all instances, activation of MAPKAPK2 in perfused hearts was inhibited by %%%SB203580%%%, an inhibitor of %%%p38%%%-MAPKs. Perfusion of hearts at high aortic pressure (20 kilopascals) also activated the SRMAPKs and MAPKAPK2. Free radical trapping agents (dimethyl sulfoxide and N-t-butyl-alpha-phenyl nitrone) inhibited the activation of SR-MAPKs and MAPKAPK2 by ischemia/reperfusion. These data are consistent with a role for reactive oxygen species in the activation of SR-MAPKs during ischemia/reperfusion.

4/7/1916
DIALOG(R)File 5:Biosis Previews(R)

0011430172 BIOSIS NO.: 199800224419
Mitogen-activated protein kinases activated by lipopolysaccharide and beta-amyloid in cultured rat microglia
AUTHOR: Pyo Hankyoung; Jou Ilo; Jung Soyoung; Hong Sumin; Joe Eun-Hye (Reprint)
AUTHOR ADDRESS: Dep. Pharmacol., Ajou Univ. Sch. Med., san-5 Woncheon-dong Paldal-gu, Suwon, Kyunggi-do 442-749, South Korea**South Korea
JOURNAL: Neuroreport 9 (5): p871-874 March 30, 1998 1998
MEDIUM: print
ISSN: 0959-4965
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To test whether mitogen-activated protein kinases (MAPKs) are involved in microglial activation, pure microglia prepared from 1- to 3-day-old rat brains were activated with either 100 ng/ml lipopolysaccharide (LPS) or 5 nM synthetic beta-amyloid (Abeta) (25-35). The patterns of MAPK activation following LPS and Abeta treatment were very similar. Three MAPK subtypes, %%%p38%%%, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) were activated within 15 min and the activities of %%%p38%%% and ERK were rapidly reduced to background level within 30 min while that of JNK was maintained for over 1 h. Both inhibitors of %%%p38%%% (%%%SB203580%%%) and ERK pathway (PD098059) reduced LPS-induced nitric oxide (NO) release and AP-induced tumor necrosis factor-alpha (TNF-alpha) release. Furthermore, co-treatment of %%%SB203580%%% and PD098059 additively reduced NO and TNF-alpha release. These results suggest that MAPK, at least %%%p38%%% and ERK, mediate LPS-, and Abeta-induced microglial activation.

4/7/1917
DIALOG(R)File 5:Biosis Previews(R)

0011428300 BIOSIS NO.: 199800222547
The phosphorylation of eukaryotic initiation factor eIF4E in resposne to phorbol esters, cell stresses, and cytokines is mediated by distinct MAP kinase pathways
AUTHOR: Wang Xuemin; Flynn Andrea; Waskiewicz Andrew J; Webb Benjamin L J; Vries Robert G; Baines Ian A; Cooper Jonathan A; Proud Christopher G (Reprint)
AUTHOR ADDRESS: Dep. Anatomy and Physiol., Med. Sci., Inst., Univ. Dundee, Dundee, DD1 4HN, UK**UK
JOURNAL: Journal of Biological Chemistry 273 (16): p9373-9377 April 17, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Initiation factor eIF4E binds to the 5'-cap of eukaryotic mRNAs and plays a key role in the mechanism and regulation of translation. It may be regulated through its own phosphorylation and through inhibitory binding proteins (4E-BPs), which modulate its availability for initiation complex assembly. eEF4E phosphorylation is enhanced by phorbol esters. We show, using specific inhibitors, that this involves both the %%%p38%%% mitogen-activated protein (MAP) kinase and Erk signaling pathways. Cell stresses such as arsenite and anisomycin and the cytokines tumor necrosis factor-alpha and interleukin-1beta also cause increased phosphorylation of eIF4E, which is abolished by the specific %%%p38%%% MAP kinase inhibitor, %%%SB203580%%%. These changes in eIF4E phosphorylation parallel the activity of the eIF4E kinase, Mnk1. However other stresses

such as heat shock, sorbitol, and H2O2, which also stimulate %%%p38%%% MAP kinase and increase Mnk1 activity, do not increase phosphorylation of eIF4E. The latter stresses increase the binding of eIF4E to 4E-BP1, and we show that this blocks the phosphorylation of eIF4E by Mnk1 in vitro, which may explain the absence of an increase in eIF4E phosphorylation under these conditions.

4/7/1918
DIALOG(R)File 5:Biosis Previews(R)

0011428139 BIOSIS NO.: 199800222386
Tumor necrosis factor-alpha induces interleukin-6 production and integrin ligand expression by distinct transduction pathways
AUTHOR: De Cesaris Paola; Starace Donatella; Riccioli Anna; Padula Fabrizio ; Filippini Antonio; Ziparo Elio (Reprint)
AUTHOR ADDRESS: Dep. Histol. Med. Embryol., Univ. Rome "La Sapienza", Via A. Scarpa 16, 00161 Rome, Italy**Italy
JOURNAL: Journal of Biological Chemistry 273 (13): p7566-7571 March 27, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tumor necrosis factor-alpha (TNF-alpha) is a pleiotropic cytokine that elicits a large number of biological effects. However, the intracellular signaling mechanisms that are responsible for the TNF-alpha effects remain largely unknown. We have previously demonstrated that cultured mouse Sertoli cells, after TNF-alpha treatment, increase the surface expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) and interleukin-6 (IL-6) production (Riccioli, A., Filippini, A., De Cesaris, P., Barbacci, E., Stefanini, M., Starace, G., and Ziparo, E. (1995) Proc. Natl Acad. Sci. U.S.A. 92,5808-5812). Here, we show that, in cultured Sertoli cells, TNF-alpha activates the mitogen-activated protein kinase pathway (%%%p38%%%, c-Jun N-terminal protein kinase/stress-activated protein kinase, and the p42/p44 mitogen-activated protein kinases) as revealed by an increased phosphorylation of %%%p38%%%, activating transcription factor-2, c-Jun, and Elk-1. Furthermore, our data indicate that the biological effects induced by TNF-alpha in Sertoli cells (enhancement of ICAM-1, VCAM-1, and IL-6 expression) depend on the activation of different signaling pathways. %%%SB203580%%%, a highly specific %%%p38%%% inhibitor, does not affect ICAM-1 and VCAM-1 expression, but strongly inhibits IL-6 production. Moreover, interferon-gamma, which up-regulates adhesion molecule expression and reduces IL-6 production, does not induce phosphorylation of %%%p38%%%. Our data strongly support the hypothesis that, in response to TNF-alpha, activation of %%%p38%%% leads to IL-6 production, whereas ICAM-1 and VCAM-1 expression could be induced by activation of the c-Jun N-terminal protein kinase/stress-activated protein kinase pathway.

4/7/1919
DIALOG(R)File 5:Biosis Previews(R)

0011416916 BIOSIS NO.: 199800211163
Lysophosphatidic acid-mediated signal-transduction pathways involved in the induction of the early-response genes prostaglandin G/H synthase-2 and Egr-1: A critical role for the mitogen-activated protein kinase %%%p38%%% and for Rho proteins
AUTHOR: Reiser Christian O A (Reprint); Lanz Thomas; Hofmann Fred; Hofer Gerhard; Rupprecht Harald D; Goppelt-Struebe Margarete
AUTHOR ADDRESS: Medizinische Klinik IV, Univ. Erlangen-Nuernberg, Loschgestr. 8, D-91054 Erlangen, Germany**Germany
JOURNAL: Biochemical Journal 330 (3): p1107-1114 March 15, 1998 1998
MEDIUM: print
ISSN: 0264-6021

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: During inflammatory processes of the kidney, lesions of the glomerulus lead to aggregation of thrombocytes and infiltration of macrophages, which can release bioactive mediators. One of these important signaling molecules is lysophosphatidic acid (LPA). Incubation of rat mesangial cells with LPA induced mRNA and protein expression of the early-response genes pghs-2 (for prostaglandin G/H synthase-2/cyclo-oxygenase-2) and egr-1. As shown by antisence experiments, induction of egr-1 was related to the strong mitogenic effect of LPA. LPA-mediated gene expression was inhibited by pertussis toxin, indicating coupling to G-proteins of the G1 family. Specific inhibition of proteins of the small G-protein subfamily Rho with toxin B from Clostridium difficile led to changes in mesangial cell morphology without induction of apoptosis. LPA-mediated expression of pghs-2 and egr-1 was reduced to base-line levels by toxin B, indicating a role for Rho proteins in LPA-mediated gene induction. Of the two mitogen-activated protein kinase (MAPK) pathways investigated, the MAPK kinase-extracellular signal-regulated kinase pathways was involved in the induction of both pghs-2 and egr-1 mRNA expression, as shown by the inhibitory effect of PD98059. Activation of the MAPK %%%p38%%%, however, was only related to pghs-2 expression whereas egr-1 expression was not affected by treatment of mesangial cells with the specific inhibitor %%%SB203580%%%. Taken together our data provide evidence that LPA-mediated activation of MAPK kinase and Rho proteins leads to the induction of the functionally distinct early-response genes pghs-2 and egr-1, whereas activation of MAPK %%%p38%%% revealed considerable differences between the regulation of these two genes.

4/7/1920
DIALOG(R)File 5:Biosis Previews(R)

0011402390 BIOSIS NO.: 199800196637
SB202190 and %%%SB203580%%% inhibit TPA- or EGF-induced AP-1 activation and cell transformation without inhibition of %%%P38%%% kinase
AUTHOR: Zheng Z (Reprint); Ma W-Y; Huang C; Dong Z
AUTHOR ADDRESS: Henan Inst. Drug Administration, Zheng-zhou, China**China
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 39 p406 March, 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 89th Annual Meeting of the American Association for Cancer Research New Orleans, Louisiana, USA March 28-April 1, 1998; 19980328
SPONSOR: American Association for Cancer Research
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

4/7/1921
DIALOG(R)File 5:Biosis Previews(R)

0011384645 BIOSIS NO.: 199800178892
Hyperosmotic induction of the mitogen-activated protein kinase phosphatase MKP-1 in H4IIE rat hepatoma cells
AUTHOR: Schliess Freimut; Heinrich Sabine; Haeussinger Dieter (Reprint)
AUTHOR ADDRESS: Med. Einrichtungen Heinrich-Heine Univ., Klinik Gastroenterologie, Moorenstrasse 5, D-40225 Duesseldorf, Germany**Germany
JOURNAL: Archives of Biochemistry and Biophysics 351 (1): p35-40 March 1, 1998 1998
MEDIUM: print
ISSN: 0003-9861
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The action of hyperosmotic stress on the MAP kinase phosphatase MKP-1 mRNA expression was studied in H4IIE rat hepatoma cells. Hyperosmotic (405 mosmol/L) challenge of the cells led to a transient expression of MKP-1 mRNA, which was maximal after 6-8 h and disappeared completely after 24 h. Hyperosmotic MKP-1 mRNA induction was preceded by a transient activation of the MAP kinases Erk-1, Erk-2, and JNK-2, which were not prerequisite for MKP-1 mRNA accumulation. However, the hyperosmolarity-induced MKP-1 mRNA expression was sensitive to antioxidants and to inhibition of %%%p38%%% by %%%SB203580%%%. A reduced sensitivity of Erk-1/Erk-2 to other stimuli was found after prolonged hyperosmotic exposure. The data are consistent with a hyperosmolarity-induced MKP-1 expression via reactive oxygen intermediates and %%%p38%%%, which may participate in the termination of MAP kinase activation and contribute to desensitization of the MAP kinases after prolonged hyperosmotic exposure of the cells.

4/7/1922
DIALOG(R)File 5:Biosis Previews(R)

0011375428 BIOSIS NO.: 199800169675
Extracellular signal-regulated kinase and %%%p38%%% subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-alpha gene expression in endotoxin-stimulated primary glial cultures
AUTHOR: Bhat Narayan R (Reprint); Zhang Peisheng; Lee John C; Hogan Edward L
AUTHOR ADDRESS: Dep. Neurol., Med. Univ. S.C., 171 Ashley Ave., Charleston, SC 29425, USA**USA
JOURNAL: Journal of Neuroscience 18 (5): p1633-1641 March 1, 1998 1998
MEDIUM: print
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Tumor necrosis factor-alpha (TNFalpha) and nitric oxide (NO), the product of inducible NO synthase (iNOS), mediate inflammatory and immune responses in the CNS under a variety of neuropathological situations. They are produced mainly by "activated" astrocytes and microglia, the two immune regulatory cells of the CNS. In this study we have examined the regulation of TNFalpha and iNOS gene expression in endotoxin-stimulated primary glial cultures, focusing on the role of mitogen-activated protein (MAP) kinase cascades. The bacterial lipopolysaccharide (LPS) was able to activate extracellular signal-regulated kinase (ERK) and %%%p38%%% kinase subgroups of MAP kinases in microglia and astrocytes. ERK activation was sensitive to PD98059, the kinase inhibitor that is specific for ERK kinase. The activity of %%%p38%%% kinase was inhibited by %%%SB203580%%%, a member of the novel class of cytokine suppressive anti-inflammatory drugs (CSAIDs), as revealed by blocked activation of the downstream kinase, MAP kinase-activated protein kinase-2. The treatment of glial cells with either LPS alone (microglia) or a combination of LPS and interferon-gamma (astrocytes) resulted in an induced production of NO and TNFalpha. The two kinase inhibitors, at micromolar concentrations, individually suppressed and, in combination, almost completely blocked glial production of NO and the expression of iNOS and TNFalpha, as determined by Western blot analysis. Reverse transcriptase-PCR analysis showed changes in iNOS mRNA levels that paralleled iNOS protein and NO while indicating a lack of effect of either of the kinase inhibitors on TNFalpha mRNA expression. The results demonstrate key roles for ERK and %%%p38%%% MAP kinase cascades in the transcriptional and post-transcriptional regulation of iNOS and TNFalpha gene expression in endotoxin-activated glial cells.

4/7/1923
DIALOG(R)File 5:Biosis Previews(R)

0011340985 BIOSIS NO.: 199800135232
%%%p38%%% and extracellular signal-regulated kinase mitogen-activated protein kinase pathways are required for nuclear factor-kappaB p65 transactivation mediated by tumor necrosis factor
AUTHOR: Vanden Berghe Wim; Plaisance Stephane; Boone Elke; De Bosscher Karolien; Schmitz M Lienhard; Fiers Walter; Haegeman Guy (Reprint)
AUTHOR ADDRESS: Lab. Mol. Biol., K. L. Ledeganckstraat 35, B-9000 Gent, Belgium**Belgium
JOURNAL: Journal of Biological Chemistry 273 (6): p3285-3290 Feb. 6, 1998
1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Interleukin-6 (IL-6) is a pleiotropic cytokine, which is involved in inflammatory and immune responses, acute phase reactions, and hematopoiesis. In the mouse fibrosarcoma cell line L929, the nuclear factor (NF)-kappaB plays a crucial role in IL-6 gene expression mediated by tumor necrosis factor (TNF). The levels of the activated factor do not, however, correlate with the variations of IL-6 gene transcription; therefore, other factors and/or regulatory mechanisms presumably modulate the levels of IL-6 mRNA production. Upon analysis of various deletion and point-mutated variants of the human IL-6 gene promoter coupled to a reporter gene, we screened for possible cooperating transcription factors. Even the smallest deletion variant, containing almost exclusively a NF-kappaB-responsive sequence preceding the IL-6 minimal promoter, as well as a recombinant construction containing multiple kappaB-motifs, could still be stimulated with TNF. We observed that the %%%p38%%% mitogen-activated protein kinase (MAPK) inhibitor %%%SB203580%%% was able to repress TNF-stimulated expression of the IL-6 gene, as well as of a kappaB-dependent reporter gene construct, without affecting the levels of NF-kappaB binding to DNA. Furthermore, we clearly show that, using a nuclear Gal4 "one-hybrid" system, the MAPK inhibitors %%%SB203580%%% and PD0980589 have a direct repressive effect on the transactivation potential of the p65 kappaB subunit. Therefore, we conclude that, in addition to cytoplasmic activation and DNA binding of NF-kappaB, the %%%p38%%% and extracellular signal-regulated kinase MAPK pathways act as necessary cooperative mechanisms to regulate TNF-induced IL-6 gene expression by modulating the transactivation machinery.

0011297760 BIOSIS NO.: 199800092007
Selective activation of %%%p38%%% mitogen-activated protein (MAP) kinase isoforms by the MAP kinase kinases MKK3 and MKK6
AUTHOR: Enslen Herve; Raingeaud Joel; Davis Roger J (Reprint)
AUTHOR ADDRESS: Howard Hughes Med. Inst., Program Molecular Med., Univ. Massachusetts Med. Sch., 373 Plantation St., Worcester, MA 01605, USA** USA
JOURNAL: Journal of Biological Chemistry 273 (3): p1741-1748 Jan. 16, 1998
1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The cellular response to treatment with proinflammatory cytokines or exposure to environmental stress is mediated, in part, by the %%%p38%%% group of mitogen-activated protein (MAP) kinases. We report the molecular cloning of a novel isoform of %%%p38%%% MAP kinase, p38beta2. This %%%p38%%% MAP kinase, like p38a, is inhibited by the pyridinyl imidazole drug %%%SB203580%%%. The %%%p38%%% MAP kinase kinase MKK6 is identified as a common activator of p38alpha, p38beta2, and p38gamma MAP kinase isoforms, while MKK3 activates only p38alpha and p38gamma MAP kinase isoforms. The MKK3 and MKK6 signal transduction pathways are

therefore coupled to distinct, but overlapping, groups of %%%p38%%% MAP kinases.

4/7/1925
DIALOG(R)File 5:Biosis Previews(R)

0011297610 BIOSIS NO.: 199800091857
The stress inducer arsenite activates mitogen-activated protein kinases extracellular signal-regulated kinases 1 and 2 via a MAPK kinase 6/ %%%p38%%%-dependent pathway
AUTHOR: Ludwig Stephan; Hoffmeyer Angelika; Goebeler Matthias; Killian Karin; Haefner Heide; Neufeld Bernd; Han Jiahuai; Rapp Ulf R (Reprint)
AUTHOR ADDRESS: Inst. Med. Strahlenkunde Zellforschung, MSZ, Univ. Wuerzburg, Versbacher Strasse 5, D-97078 Wuerzburg, Germany**Germany
JOURNAL: Journal of Biological Chemistry 273 (4): p1917-1922 Jan. 23, 1998 1998
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cell response to a wide variety of extracellular signals is mediated by either mitogenic activation of the Raf/MEK/ERK kinase cascade or stress-induced activation of the mitogen-activated protein kinase (MAPK) family members c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) or %%%p38%%%. We have examined communications between these stress- and mitogen-induced signaling pathways. We show here that the stress cascade activator arsenite activates extracellular signal-regulated kinase (ERR) in addition to %%%p38%%% albeit with different kinetics. Whereas %%%p38%%% is an early response kinase, ERK activation occurs with delayed time kinetics at 2-4 h. We observed activation of ERK upon arsenite treatment in many different cell lines. ERR activation is strongly enhanced by overexpression of %%%p38%%% and mitogen-activated protein kinase 6 (MKK6) but is blocked by dominant negative kinase versions of %%%p38%%% and MKK6 or the specific %%%p38%%% inhibitor %%%SB203580%%%. Arsenite-induced ERK activation is mediated by Ras, Raf, and MEEK but appears to be independent of de novo protein synthesis. These data provide the first evidence for a %%%p38%%% dependent activation of the mitogenic kinase cascade in stress-stimulated cells.

? t s5/7/1-57

5/7/1
DIALOG(R)File 5:Biosis Previews(R)

0015120223 BIOSIS NO.: 200500027288
Novel homozygous p.E64D mutation in DJ1 in early onset Parkinson disease (PARK7)
AUTHOR: Hering Robert; Strauss Karsten M; Tao Xiao; Bauer Andreas; Woitalla Dirk; Mietz Eva-Maria; Petrovic Slobodanka; Bauer Peter; Schaible Wilhelm ; Mueller Thomas; Schoels Ludger; Klein Christine; Berg Daniela; Meyer Philipp T; Schulz Joerg B; Wollnik Bernd; Tong Liang; Krueger Rejko; Riess Olaf (Reprint)
AUTHOR ADDRESS: Dept Med Genet, Univ Tubingen, Calwerstr 7, D-72076, Tubingen, Germany**Germany
AUTHOR E-MAIL ADDRESS: olaf.riess@med.uni-tuebingen.de
JOURNAL: Human Mutation 24 (4): p321-329 2004 2004
MEDIUM: print
ISSN: 1059-7794
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the %%%parkin%%% gene have been identified as a common cause of autosomal recessive inherited Parkinson disease (PD) associated with early disease manifestation. However, based on linkage

Parkin x Birley

data, mutations in other genes contribute to the genetic heterogeneity of early-onset PD (EOPD). Recently, two mutations in the DJ1 gene were described as a second cause of autosomal recessive EOPD (PARK7). Analyzing the PARK7/DJ1 gene in 104 EOPD patients, we identified a third mutation, c.192G>C (p.E64D), associated with EOPD in a patient of Turkish ancestry and characterized the functional significance of this amino acid substitution. In the patient, a substantial reduction of dopamine uptake transporter (DAT) %%%binding%%% was found in the striatum using (18F)FP-CIT and PET, indicating a serious loss of presynaptic dopaminergic afferents. His sister, homozygous for E64D, was clinically unaffected but showed reduced dopamine uptake when compared with a clinically unaffected brother, who is heterozygous for E64D. We demonstrate by crystallography that the E64D mutation does not alter the structure of the DJ1 protein, however we observe a tendency towards decreased levels of the mutant protein when overexpressed in HEK293 or COS7 cells. Using immunocytochemistry in contrast to the homogenous nuclear and cytoplasmic staining in HEY, 293 cells overexpressing wild,type DJ1, about 5% of the cells expressing E64D and up to 80% of the cells expressing the recently described L166P mutation displayed a predominant nuclear localization of the mutant DJ1 protein. Copyright 2004 Wiley-Liss, Inc.

5/7/2
DIALOG(R)File 5:Biosis Previews(R)

0015021025 BIOSIS NO.: 200400391814
Structure of the C-terminal RING finger from a RING-IBR-RING/TRIAD motif reveals a novel zinc-%%%binding%%% domain distinct from a RING
AUTHOR: Capili Allan D; Edghill E L; Wu Kenneth; Borden Katherine L B (Reprint)
AUTHOR ADDRESS: Struct Biol ProgramDept Physiol and Biophys, CUNY Mt Sinai Sch Med, New York, NY, 10029, USA**USA
AUTHOR E-MAIL ADDRESS: katherine.borden@mssm.edu
JOURNAL: Journal of Molecular Biology 340 (5): p1117-1129 July 23, 2004 2004
MEDIUM: print
ISSN: 0022-2836 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The really interesting new gene (RING) family of proteins contains over 400 members with diverse physiological functions. A subset of these domains is found in the context of the RING-IBR-RING/TRIAD motifs which function as E3 ubiquitin ligases. Our sequence analysis of the C-terminal RING (RING2) from this motif show that several metal ligating and hydrophobic residues critical for the formation of a classical RING 2 cross-brace structure are not present. Thus, we determined the structure of the RING2 from the RING-IBR-RING motif of HHARI and showed.. that RING2 has a completely distinct topology from classical RINGs. Notably, RING2 binds only one zinc atom per monomer rather than two and uses a different hydrophobic network to that of classical RINGs. Additionally, this RING2 topology is novel, bearing slight resemblance to zinc-ribbon motifs around the zinc site and is different from the topologies of the zinc %%%binding%%% sites found in RING and PHDs. We demonstrate that RING2 acts as an E3 ligase in vitro and using mutational analysis deduce the structural features required for this activity. Further, mutations in the RING-IBR-RING of %%%Parkin%%% cause a rare form of Parkinsonism and these studies provide an explanation for those mutations that occur in its RING2. From a comparison of the RING2 structure with those reported for RINGs, we infer sequence determinants that allow discrimination between RING2 and RING domains at the sequence analysis level. Copyright 2004 Elsevier Ltd. All rights reserved.

5/7/3
DIALOG(R)File 5:Biosis Previews(R)

0014978672 BIOSIS NO.: 200400349461
N-myc regulates %%%parkin%%% expression
AUTHOR: West Andrew B (Reprint); Kapatos Gregory; O'Farrell Casey; Gonzalez-de-Chavez Fanny; Chiu Kelvin; Farrer Matthew J; Maidment Nigel T
AUTHOR ADDRESS: 760 Westwood Plaza,Box 77, Los Angeles, CA, 90024, USA**USA
AUTHOR E-MAIL ADDRESS: abwest7@yahoo.com
JOURNAL: Journal of Biological Chemistry 279 (28): p28896-28902 July 9, 2004 2004
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the %%%parkin%%% gene are common in early-onset and familial Parkinson's disease (PD), and the %%%parkin%%% protein interacts in the ubiquitin-proteasome system as an E3 ligase. However, the regulatory pathways that govern %%%parkin%%% expression are unknown. In this study, we showed that a phylogenetically conserved N-myc %%%binding%%% site in the bi-directional %%%parkin%%% promoter interacted with myc-family transcription factors in reporter assays, and N-myc bound to the %%%parkin%%% promoter in chromatin immunoprecipitation assays and repressed transcription activity. %%%Parkin%%% expression was inversely correlated with N-myc levels in the developing mouse and human brain, in human neuroblastoma cell lines with various levels of n-myc amplification, and in an inducible N-myc cell line. Although %%%parkin%%% and N-myc expression were dramatically altered upon retinoic acid-induced differentiation of a human neuroblastoma cell line, modulation of %%%parkin%%% expression did not significantly affect either rates of cellular proliferation or levels of cyclin E. Analysis of additional genes associated with familial PD revealed a shared basis of transcription regulation mediated by N-myc and the cell cycle. Our results, in combination with functional knowledge of the proteins encoded by these genes, suggest a common pathway linking together PD, the ubiquitin-proteasome system, and cell cycle control.

5/7/4
DIALOG(R)File 5:Biosis Previews(R)

0014882012 BIOSIS NO.: 200400252769
Endoplasmic reticulum (ER) stress as the signaling mechanism of neurodegeneration.
AUTHOR: Takahashi Ryosuke (Reprint)
AUTHOR ADDRESS: Lab Motor System Neurodegeneration, RIKEN Brain Science Institute (BSI), Wako, 351-0198, Japan**Japan
JOURNAL: Journal of Pharmacological Sciences 94 (Supplement 1): p30P 2004 2004
MEDIUM: print
CONFERENCE/MEETING: 77th Annual Meeting of the Japanese Pharmacological Society Osaka, Japan March 08-10, 2004; 20040308
SPONSOR: Japanese Pharmacological Society
ISSN: 1347-8613 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/7/5
DIALOG(R)File 5:Biosis Previews(R)

0014834059 BIOSIS NO.: 200400201692
The microtubule associated protein, tau, is a substrate of CHIP.
AUTHOR: Petrucelli L N (Reprint); Grover A (Reprint); Kehoe K (Reprint); DeLucia M (Reprint); Taylor J (Reprint); McGowan E (Reprint); Lewis J (Reprint); Hardy J; Dawson T; Wolozin B; Hutton M (Reprint)
AUTHOR ADDRESS: NeuroGenet., Mayo Clin., Jacksonville, FL, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner

2003 pAbstract No. 558.5 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Molecular chaperones and ubiquitin ligases have been implicated in several neurodegenerative diseases are characterized by accumulation of protein aggregates (e. g. tau and synuclein). These aggregates have been shown in various experimental systems to increase toxicity and/or increase proteasome impairment. It remains unclear whether chaperones/ligases also play a role in tau metabolism. Here, we report that CHIP directly binds to tau, Hsp70 and %%%Parkin%%% in vitro and in vivo. CHIP specifically binds to the microtubule %%%binding%%% domain of tau. CHIP promotes the ubiquitination and degradation of the tau protein. Further, tau lesions in several tauopathies, including Alzheimer's and Pick's disease are immunopositive for CHIP. Overexpresson of wildtype and mutant tau increases sensitivity to proteasome inhibitors by decreasing proteasome function. Treatment of cells with geldanamycin rescues toxicity and proteasome impairment. Here, we show that the microtubule associated protein, tau is a substrate of CHIP and the accumulation of which may cause selective neuronal degeneration.

5/7/6
DIALOG(R)File 5:Biosis Previews(R)

0014834056 BIOSIS NO.: 200400201689
O-glycosylation of alpha-synuclein in primate brain: a substantia nigra modification essential for %%%Parkin%%% %%%binding%%%.
AUTHOR: Schlossmacher M G (Reprint); Shimura H (Reprint); Rasakham S (Reprint); Chan J; Sutton-Smith M; Dell A; Madras B; Kosik K (Reprint); Selkoe D (Reprint)
AUTHOR ADDRESS: Ctr. for Neurol. Dis., Brigham and Womens Hosp, Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 558.2 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We previously reported a link between alpha-synuclein (alphaS) and %%%parkin%%%, each of which is associated with Parkinson disease (PD). We have now extended this work to show that glycosylated alphaS is detectable in human and monkey brains, occurring as 20-22 kDa isoforms. cDNAs generated from cynomologus and small squirrel monkey brain revealed 100 % aa sequence identity with human alphaS, in contrast to the 7 aa differences in mouse and rat, which have no detectable alphaSglyc (even in human alphaS transgenic mice). In human cortex, alphaSp22glyc accounted for <1 % of monomeric alphaS detectable by Western blotting. Although human midbrain contained apprx70 % less unglycosylated alphaSp16 than did cortex, the relative amount of alphaSp22glyc was apprx5-fold higher in Substantia nigra than cortex. Cortex from subjects with PD, dementia with Lewy bodies and multiple system atrophy also contained alphaSp22glyc. Lectin-%%%binding%%% assays and glycosidase treatments revealed a mucin-type glycosylation of alphaS: an O-linked disaccharide, N-acetylgalactosamine-alpha-1,4-galactosamine, with terminal sialic acid modification. Mass spectrometry of alphaSp22glyc purified to homogeneity from human cortex identified 134 of the 140 aa, suggesting that the O-glycosylation occurs at the hydroxyl groups of Ser9 and/or Thr22. Importantly, only glycosylated alphaS (but not human alphaSp16) interacted with %%%parkin%%% in vitro. Our data suggest that a small fraction of primate brain alphaS can undergo O-glycosylation, perhaps via

passage through the secretory pathway, representing a rare but obligatory modification for subsequent recognition of alphaSp22glyc by %%%parkin%%%. This posttranslational modification of alphaS may play a role in the pathogenesis of PD.

5/7/7
DIALOG(R)File 5:Biosis Previews(R)

0014831791 BIOSIS NO.: 200400199424
Tubulin - %%%binding%%% domains of %%%Parkin%%%.
AUTHOR: Yang F (Reprint); Zhao J (Reprint); Ren Y (Reprint); Feng J (Reprint)
AUTHOR ADDRESS: Dept. of Physiology and Biophysics, State Univ. of New York at Buffalo, Buffalo, NY, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2003 pAbstract No. 408.8 2003 2003
MEDIUM: e-file
CONFERENCE/MEETING: 33rd Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 08-12, 2003; 20031108
SPONSOR: Society of Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Our previous studies have shown that %%%parkin%%% binds to microtubules and alpha/beta tubulin heterodimers with very high affinity (Ren et al. J. Neurosci. 23:3316-3324). In order to identify regions of %%%parkin%%% that are responsible for the interaction with tubulin and microtubules, we transfected various domains of %%%parkin%%% into HEK293T cells and assessed their ability to co-immunoprecipitate endogenous tubulin heterodimers. Our preliminary results showed that the second RING finger domain strongly bound to tubulin heterodimers, whereas the first RING finger and the N-terminal half of the protein provided additional weaker %%%binding%%%. In contrast, the IBR region did not bind to tubulin heterodimers appreciably. Our data suggest that the tight %%%binding%%% between %%%parkin%%% and tubulin may be attributable to multiple interactions between several domains of %%%parkin%%% and tubulin. Further analyses are underway to examine the ability of these tubulin-%%%binding%%% domains to co-assemble with microtubules.

5/7/8
DIALOG(R)File 5:Biosis Previews(R)

0014805562 BIOSIS NO.: 200400176319
CHIP-Hsc70 complex ubiquitinates phosphorylated tau and enhances cell survival.
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JOURNAL: Journal of Biological Chemistry 279 (6): p4869-4876 February 6, 2004 2004
MEDIUM: print
ISSN: 0021-9258
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The microtubule-%%%binding%%% protein tau has been implicated in the neurofibrillary pathology of Alzheimer's disease. Within affected cells, ubiquitinated and hyperphosphorylated tau assembles into massive filamentous polymers. Eventually these tangle-bearing neurons die. The formation of neurofibrillary tangles closely parallels the progression and anatomic distribution of neuronal loss in Alzheimer's disease, suggesting that these lesions play a role in the disease pathogenesis. Mutations in the human tau gene cause autosomal dominant

neurodegenerative disorders. These and other neurodegenerative conditions are also characterized by extensive neurofibrillary pathology. The mechanisms underlying tau-mediated neurotoxicity remain unclear; however, phosphorylated tau is a strong candidate for a toxic molecule, particularly those isoforms phosphorylated by the kinases glycogen synthase kinase 3beta and Cdk5. Here we show that Alzheimer tau binds to Hsc70, and its phosphorylation is a recognition requirement for the addition of ubiquitin (Ub) by the E3 Ub ligase CHIP (carboxyl terminus of the Hsc70-interacting protein) and the E2 conjugating enzyme UbcH5B. Other E3 Ub ligases including %%%parkin%%% and Cbl failed to ubiquitinate phosphorylated tau. CHIP could rescue phosphorylated tau-induced cell death, and therefore the CHIP-Hsc70 complex may provide a new therapeutic target for the tauopathies.

5/7/9
DIALOG(R)File 5:Biosis Previews(R)

0014780782 BIOSIS NO.: 200400147443
The ubiquitin ligase Triad1 inhibits clonogenic growth of primary immature bone marrow cells.
AUTHOR: van der Reijden Bert A (Reprint); Marteijn Jurgen A F (Reprint); van Emst Liesbeth (Reprint); de Witte Theo M (Reprint); Jansen Joop H (Reprint)
AUTHOR ADDRESS: Hematology, UMC Nijmegen, Nijmegen, Netherlands** Netherlands
JOURNAL: Blood 102 (11): p576a-577a November 16, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the American Society of Hematology San Diego, CA, USA December 06-09, 2003; 20031206
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Treatment of acute promyelocytic leukemia (APL) with all-trans retinoic acid (ATRA) induces terminal granulocytic differentiation of the malignant cells. The genes which initiate this differentiation process remain largely unknown. We have identified a novel gene (Triad1) which appeared to be upregulated during the ATRA induced differentiation of APL cells. Triad1 codes for a 493 aa protein, which consists of a N-terminal acidic domain and two C-terminal coiled coils. The central part of the protein harbors a 200 aa tripartite TRIAD structure that consists of two RING fingers that flank a DRIL/IBR (double RING finger linked, in between ring finger) domain. To date, 10 human proteins with a TRIAD structure have been identified. Amongst these is %%%parkin%%%, a protein mutated in juvenile forms of Parkinsons and parc, a protein that regulates p53 activity by sequestering it in the cytoplasm. To study the role of Triad1 in hematopoiesis we tested whether it affects clonogenic growth of primary immature murine bone marrow cells. These cells were retrovirally transduced with pLZRS-derived viruses containing a GFP-IRES-Triad1 sequence. GFP positive cells were sorted by FACS and used in semi-solid colony assays (CFU-GM). Compared to empty vector controls (GFP alone), Triad1 expression resulted in more than 80% inhibition of clonogenic growth (n=4). Moreover, colonies derived from Triad1 transduced cells were significantly smaller compared to empty vector controls. To examine the growth inhibition in more detail we studied proliferation, cell cycle progression (DNA histograms), differentiation (Mac1/Gr1 expression) and apoptosis (annexin V positivity) of transduced (GFP+) bone marrow cells in liquid medium over a period of seven days. Compared to empty vector control, Triad1 expression resulted in a 17-fold reduction of absolute cell numbers after 4 days of culture. This was accompanied by a marked increase in the % of cells in G1/G0 and annexin V positivity and decrease in the % of Mac1 positive cells (72 vs 52% in G1/G0; 28 vs 13% Annexin V+; 38 vs 78% Mac1+ and 65 vs 71% Gr1+ cells after 4 days of culture for Triad1 and empty vector positive populations, respectively). To determine whether the conserved TRIAD structure was necessary for the observed effects we constructed three different Triad1 mutants in which either one of three conserved cys/his residues of the N-terminal RING finger were

changed into ala. In contrast to wild type Triad1, the mutants did not affect clonogenic growth of primary murine bone marrow cells revealing a crucial role for the N-terminal RING finger of Triad1 in the regulation of proliferation and differentiation of myeloid progenitors. Several RING finger proteins have recently been shown to function as ubiquitin ligases. These proteins catalyze the conjugation of ubiquitin to substrate proteins which mark them for targeted degradation by the 26S proteasome. The ubiquitin ligases act in concert with ubiquitin conjugating enzymes (Ubcs) that bind to the ligases. In most ubiquitin ligases the RING finger is involved in %%%binding%%% Ubcs. Because Triad1 contains two RING fingers, we tested a panel of Ubcs (Cdc34,UbcH5,6,7,8,10 and Bendless) in yeast-two-hybrid assays for interaction with Triad1. Of these, Bendless, UbcH6 and -7 were found to interact with Triad1. The latter two interactions were confirmed by GST-Triad1 pull down experiments using cell lysates from APL cells. These data define a role for Triad1 in hematopoiesis and suggest that Triad1 inhibits clonogenic growth by targeted destruction of specific substrate proteins through the ubiquitin-proteasome pathway.

5/7/10
DIALOG(R)File 5:Biosis Previews(R)

0014730260 BIOSIS NO.: 200400101017
Siah-1 facilitates ubiquitination and degradation of synphilin-1.
AUTHOR: Nagano Yoshito; Yamashita Hiroshi (Reprint); Takahashi Tetsuya; Kishida Shosei; Nakamura Takeshi; Iseki Eizo; Hattori Nobutaka; Mizuno Yoshikuni; Kikuchi Akira; Matsumoto Masayasu
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JOURNAL: Journal of Biological Chemistry 278 (51): p51504-51514 December 19, 2003 2003
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Parkinson's disease is a common neurodegenerative disorder characterized by loss of dopaminergic neurons and appearance of Lewy bodies, cytoplasmic inclusions that are highly enriched with ubiquitin. Synphilin-1, alpha-synuclein, and %%%Parkin%%% represent the major components of Lewy bodies and are involved in the pathogenesis of Parkinson's disease. Synphilin-1 is an alpha-synuclein-%%%binding%%% protein that is ubiquitinated by %%%Parkin%%%. Recently, a mutation in the synphilin-1 gene has been reported in patients with sporadic Parkinson's disease. Although synphilin-1 localizes close to synaptic vesicles, its function remains unknown. To investigate the proteins that interact with synphilin-1, the present study performed a yeast two-hybrid screening and identified a novel interacting protein, Siah-1 ubiquitin ligase. Synphilin-1 and Siah-1 proteins were endogenously expressed in the central nervous system and were found to coimmunoprecipitate each other in rat brain homogenate. Confocal microscopic analysis revealed colocalization of both proteins in cells. Siah-1 was found to interact with the N terminus of synphilin-1 through its substrate-%%%binding%%% domain and to specifically ubiquitinate synphilin-1 via its RING finger domain. Siah-1 facilitated synphilin-1 degradation via the ubiquitin-proteasome pathway more efficiently than %%%Parkin%%%. Siah-1 was found to not facilitate ubiquitination and degradation of wild type or mutant alpha-synuclein. Synphilin-1 inhibited high K+-induced dopamine release from PC12 cells. Siah-1 was found to abrogate the inhibitory effects of synphilin-1 on dopamine release. Such findings suggest that Siah-1 might play a role in regulation of synphilin-1 function.

5/7/11
DIALOG(R)File 5:Biosis Previews(R)

0014705144 BIOSIS NO.: 200400071400
SEPT5_v2 is a %%%parkin%%%-%%%binding%%% protein.
AUTHOR: Choi P; Snyder H; Petrucelli L; Theisler C; Chong M; Zhang Y; Lim K ; Chung K K K; Kehoe K; D'Adamio L; Lee J M; Cochran E; Bowser R; Dawson T M; Wolozin B (Reprint)
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JOURNAL: Molecular Brain Research 117 (2): p179-189 October 2003 2003
MEDIUM: print
ISSN: 0169-328X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in %%%parkin%%% are associated with various inherited forms of Parkinson's disease (PD). %%%Parkin%%% is a ubiquitin ligase enzyme that catalyzes the covalent attachment of ubiquitin moieties onto substrate proteins destined for proteasomal degradation. The substrates of %%%parkin%%%-mediated ubiquitination have yet to be completely identified. Using a yeast two-hybrid screen, we isolated the septin, human SEPT5_v2 (also known as cell division control-related protein 2), as a putative %%%parkin%%%-%%%binding%%% protein. SEPT5_v2 is highly homologous to another septin, SEPT5, which was recently identified as a target for %%%parkin%%%-mediated ubiquitination. SEPT5_v2 binds to %%%parkin%%% at the amino terminus and in the ring finger domains. Several lines of evidence have validated the putative link between %%%parkin%%% and SEPT5_v2. %%%Parkin%%% co-precipitates with SEPT5_v2 from human substantia nigra lysates. %%%Parkin%%% ubiquitinates SEPT5_v2 in vitro, and both SEPT5_v1 and SEPT5_v2 accumulate in brains of patients with ARJP, suggesting that %%%parkin%%% is essential for the normal metabolism of these proteins. These findings suggest that an important relationship exists between %%%parkin%%% and septins.

5/7/12

0014675013 BIOSIS NO.: 200400045770
Genomic organization and expression of %%%parkin%%% in Drosophila melanogaster.
AUTHOR: Bae Young-Joo; Park Kwang-Sook; Kang Soon-Ja (Reprint)
AUTHOR ADDRESS: Department of Biological Science, College of Natural Science, Ewha Womans University, Seoul, 120-750, South Korea**South Korea
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JOURNAL: Experimental & Molecular Medicine 35 (5): p393-402 October 31, 2003 2003
MEDIUM: print
ISSN: 1226-3613
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We report here the isolation, characterization on genomic structure and expression of the D. melanogaster homolog of human %%%parkin%%%. The 2,122 bp %%%parkin%%% gene sequence contains six exons that form a 1,449 bp transcript encoding a protein of 482 amino acids. 151 bp of 5' and 112 bp of 3' untranslated regions were identified by a combination of 5'-RACE/primer extension and 3'-RACE, respectively. The 5' UTR contains three transcription initiation sites. Neither a classical TATA nor a CAAT box was found in the putative promoter sequence. However, %%%binding%%% sites for AhR-Arnt, AP4, NF1 and GATA transcription factors were identified. Transient transfection analysis of the 5' UTR confirmed its promoter activity in HEK 293 cells and SH-SY5Y neuronal cells using a dual luciferase reporting system. The amino acid sequence of D. melanogaster %%%Parkin%%% exhibits 42%, 43% and 43% identity to that of human, mouse and rat, respectively, representing a 54 kDa protein band via western blot analysis. It shows a high degree of conservation in the Ubiquitin-like domain at the N-terminus (34%), the In-Between RING finger

domains (IBR, 65-69%), and the RING finger domains at the C-terminus (56-57%). The expression pattern of D. melanogaster %%%parkin%%% varies during the developmental stages, with the highest expression in the adult stage as measured by competitive RT-PCR. From immunostainings of the embryo, D. melanogaster %%%parkin%%% was expressed slightly higher in the central nervous system (brain and nerve cord) during the late embryonic stage.

5/7/13
DIALOG(R)File 5:Biosis Previews(R)

0014640106 BIOSIS NO.: 200400020863
Pael receptor, endoplasmic reticulum stress, and Parkinson's disease.
AUTHOR: Takahashi Ryosuke (Reprint); Imai Yuzuru
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JOURNAL: Journal of Neurology 250 (Suppl. 3): pIII.25-III.29 October 2003 2003
MEDIUM: print
ISSN: 0340-5354 _(ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Autosomal recessive juvenile parkinsonism (AR-JP) is caused by mutations of the %%%parkin%%% gene. %%%Parkin%%% is an E3 ubiquitin ligase that specifically recognizes its substrate protein, promoting its ubiquitination and subsequent degradation. Accordingly, we hypothesized that AR-JP may be caused by accumulation of an unidentified neurotoxic protein, which is a substrate of %%%parkin%%%. Based on this hypothesis, we cloned %%%parkin%%%-%%%binding%%% protein using a yeast two-hybrid system and identified a putative G protein-coupled receptor protein, which we named the Pael receptor (Pael-R). When overexpressed in cells, this receptor became unfolded, insoluble, and ubiquitinated. Accumulation of the insoluble Pael-R subsequently led to endoplasmic reticulum (ER) stress-induced cell death. %%%Parkin%%% specifically ubiquitinates the unfolded Pael-R and promotes its degradation, resulting in suppression of cell death induced by the accumulation of unfolded Pael-R. Moreover, insoluble Pael-R accumulates in the brains of AR-JP patients. It is highly expressed by the dopaminergic neurons of the substantia nigra, strongly suggesting that accumulation of unfolded Pael-R may lead to selective death of dopaminergic neurons in AR-JP. Recently, we identified Hsp70 and its co-chaperone CHIP as novel %%%parkin%%%-%%%binding%%% partners. We found that CHIP enhanced %%%parkin%%%-mediated ubiquitination of Pael-R. In concert with Hsp70, CHIP also enhanced the ability of %%%parkin%%% to inhibit cell death induced by Pael-R, indicating that CHIP and Hsp70 are both co-factors of %%%parkin%%%.

5/7/14
DIALOG(R)File 5:Biosis Previews(R)

0014569207 BIOSIS NO.: 200300524104
The autosomal recessive juvenile Parkinson disease gene product, %%%parkin%%%, interacts with and ubiquitinates synaptotagmin XI.
AUTHOR: Huynh Duong P; Scoles Daniel R; Nguyen Dung; Pulst Stefan M (Reprint)
AUTHOR ADDRESS: Cedars-Sinai Medical Center, 8700 Beverly Blvd, Davis Research Blvd, Room 2091, Los Angeles, CA, 90048, USA**USA
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JOURNAL: Human Molecular Genetics 12 (20): p2587-2597 15 October, 2003 2003
MEDIUM: print
ISSN: 0964-6906 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Inactivating mutations of the gene encoding %%%parkin%%% are responsible for some forms of autosomal recessive juvenile Parkinson disease. %%%Parkin%%% is a ubiquitin ligase that ubiquitinates misfolded proteins targeted for the proteasome-dependent protein degradation pathway. Using the yeast two-hybrid system and co-immunoprecipitation methods, we identified synaptotagmin XI as a protein that interacts with %%%parkin%%%. %%%Parkin%%% binds to the C2A and C2B domains of synaptotagmin XI resulting in the polyubiquitination of synaptotagmin XI. Truncated and missense mutated parkins reduce %%%parkin%%%-sytXI %%%binding%%% affinity and ubiquitination. %%%Parkin%%%-mediated ubiquitination also enhances the turnover of sytXI. In sporadic PD brain sections, sytXI was found in the core of the Lewy bodies. Since synaptotagmin XI is a member of the synaptotagmin family that is well characterized in their importance for vesicle formation and docking, the interaction with this protein suggests a role for %%%parkin%%% in the regulation of the synaptic vesicle pool and in vesicle release. Loss of %%%parkin%%% could thus affect multiple proteins controlling vesicle pools, docking and release and explain the deficits in dopaminergic function seen in patients with %%%parkin%%% mutations.

5/7/15
DIALOG(R)File 5:Biosis Previews(R)

0014555779 BIOSIS NO.: 200300511142
%%%Parkin%%% is recruited to the centrosome in response to inhibition of proteasomes.
AUTHOR: Zhao Jinghui; Ren Yong; Jiang Oian; Feng Jian (Reprint)
AUTHOR ADDRESS: Department of Physiology and Biophysics, State University of New York at Buffalo, Buffalo, NY, 14214, USA**USA
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JOURNAL: Journal of Cell Science 116 (19): p4011-4019 October 1, 2003 2003
MEDIUM: print
ISSN: 0021-9533 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Parkin%%% is a protein-ubiquitin E3 ligase linked to Parkinson's disease. Although several substrates of %%%parkin%%% have been identified, the subcellular location for %%%parkin%%% to recognize and ubiquitinate its targets is unclear. Here we report that %%%parkin%%% was accumulated in the centrosome when SH-SY5Y or transfected HEK293 cells were treated with the proteasome inhibitor lactacystin. The specific recruitment of %%%parkin%%% was dependent on concentration and duration of the treatment, and was accompanied by the centrosomal accumulation of ubiquitinated proteins and CDCrel-1, a substrate of %%%parkin%%%. The recruitment of %%%parkin%%% was apparently mediated through its %%%binding%%% to gamma-tubulin, which has been shown to accumulate in the centrosome in response to misfolded proteins. Furthermore, the effect was abrogated by the microtubule-depolymerizing drug colchicine or the microtubule-stabilizing drug taxol, which indicates that the intact microtubule network is required for the centrosomal recruitment of %%%parkin%%%. Taken together, our data suggest that the lactacystin-induced accumulation of %%%parkin%%% in the centrosome plays a significant role in the ubiquitination of misfolded substrates accumulated there. This process may provide a subcellular locale for %%%parkin%%% to ubiquitinate and degrade protein aggregates critically involved in the pathogenesis of Parkinson's disease.

5/7/16
DIALOG(R)File 5:Biosis Previews(R)

0014530024 BIOSIS NO.: 200300487681
%%%Parkin%%% and endoplasmic reticulum stress.
BOOK TITLE: Parkinson's Disease: The life cycle of the dopamine neuron
AUTHOR: Takahashi Ryosuke (Reprint); Imai Yuzuru; Hattori Nobutaka; Mizuno

Yoshikuni
BOOK AUTHOR/EDITOR: Federoff Howard J (Editor); Burke Robert E (Editor); Fahn Stanley (Editor); Fiskum Gary (Editor)
AUTHOR ADDRESS: Laboratory for Motor System Neurodegeneration, RIKEN Brain Science Institute (BSI), 2-1 Hirosawa, Wako, Saitama, 351-0198, Japan** Japan
AUTHOR E-MAIL ADDRESS: ryosuke@brain.riken.go.jp
SERIES TITLE: Annals of the New York Academy of Sciences Volume 991 p 101-106 2003
MEDIUM: print
BOOK PUBLISHER: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA
CONFERENCE/MEETING: Conference on Parkinson's Disease: The Life Cycle of the Dopamine Neuron Princeton, NJ, USA September 18-20, 2002; 20020918
SPONSOR: New York Academy of Sciences
ISSN: 0077-8923 _(ISSN print) ISBN: 1-5733-445-X (cloth)
DOCUMENT TYPE: Book Chapter; Meeting; Meeting Paper
RECORD TYPE: Citation
LANGUAGE: English

5/7/17
DIALOG(R)File 5:Biosis Previews(R)

0014509239 BIOSIS NO.: 200300464850
Innate differences in protein expression in the nucleus accumbens and hippocampus of inbred alcohol-preferring and -nonpreferring rats.
AUTHOR: Witzmann Frank A (Reprint); Li Junyu; Strother Wendy N; McBride William J; Hunter Lawrence; Crabb David W; Lumeng Lawrence; Li Ting-Kai
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JOURNAL: Proteomics 3 (7): p1335-1344 July 2003 2003
MEDIUM: print
ISSN: 1615-9853 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Two-dimensional gel electrophoresis (2-DE) was used to separate protein samples solubilized from the nucleus accumbens and hippocampus of alcohol-naive, adult, male inbred alcohol-preferring (iP) and alcohol-nonpreferring (iNP) rats. Several protein spots were excised from the gel, destained, digested with trypsin, and analyzed by mass spectrometry. In the hippocampus, 1629 protein spots were matched to the reference pattern, and in the nucleus accumbens, 1390 protein spots were matched. Approximately 70 proteins were identified in both regions. In the hippocampus, only 8 of the 1629 matched protein spots differed in abundance between the iP and iNP rats. In the nucleus accumbens, 32 of the 1390 matched protein spots differed in abundance between the iP and iNP rats. In the hippocampus, the abundances of all 8 proteins were higher in the iNP than iP rat. In the nucleus accumbens, the abundances of 31 of 32 proteins were higher in the iNP than iP rat. In the hippocampus, only 2 of the 8 proteins that differed could be identified, whereas in the nucleus accumbens 21 of the 32 proteins that differed were identified. Higher abundances of cellular retinoic acid-%%%binding%%% protein 1 and a calmodulin-dependent protein kinase (both of which are involved in cellular signaling pathways) were found in both regions of the iNP than iP rat. In the nucleus accumbens, additional differences in the abundances of proteins involved in (i) metabolism (e.g., calpain, %%%parkin%%%, glucokinase, apolipoprotein E, sorbitol dehydrogenase), (ii) cyto-skeletal and intracellular protein transport (e.g., beta-actin), (iii) molecular chaperoning (e.g., grp 78, hsc70, hsc 60, grp75, prohibitin), (iv) cellular signaling pathways (e.g., protein kinase C-%%%binding%%% protein), (v) synaptic function (e.g., complexin I, gamma-enolase, syndapin IIbb), (vi) reduction of oxidative stress (thioredoxin peroxidase), and (vii) growth and differentiation (hippocampal cholinergic neurostimulating peptide) were found. The results of this study indicate that selective breeding for disparate

alcohol drinking behaviors produced innate alterations in the expression of several proteins that could influence neuronal function within the nucleus accumbens and hippocampus.

5/7/18
DIALOG(R)File 5:Biosis Previews(R)

0014481860 BIOSIS NO.: 200300438894
Part I: %%%Parkin%%%-associated proteins and Parkinson's disease.
AUTHOR: Dev Kumlesh K (Reprint); van der Putten Herman; Sommer Bernd; Rovelli Giorgio
AUTHOR ADDRESS: Nervous System Research, Unit of Neurodegeneration, Novartis Pharma AG, CH-4002, Basel, Switzerland**Switzerland
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JOURNAL: Neuropharmacology 45 (1): p1-13 July 2003 2003
MEDIUM: print
ISSN: 0028-3908
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Parkin%%% is an E3 ligase that plays an important role in the ubiquitin/proteosome pathway responsible for protein degradation events. Mutations in %%%parkin%%% result in a loss-of-function and lead to Parkinson's disease, a progressive neurological disorder of movement. Presumably, this occurs due to the toxic build-up of proteins that are no longer effectively cleared/degraded by the %%%parkin%%%-dependent ubiqutin/proteosome pathway. To date, three types of proteins have been shown to interact with %%%parkin%%%. Firstly, the E2 ubiquitin conjugating proteins called UbcH7 and UbcH8 interact with %%%parkin%%%. Secondly, putative substrates interacting with %%%parkin%%% include a synaptic vesicle associated GTPase named CDCrel-1; a G protein-coupled receptor named Pael; a novel from of alpha-synuclein; and an alpha-synuclein interacting protein synphilin-1. Thirdly and more recently, a PDZ domain containing scaffolding protein CASK/Lin2 has been shown to interact with the PDZ %%%binding%%% motif of %%%parkin%%%. A network of PDZ-interacting proteins has potential to form a complex web of molecules that surround %%%parkin%%% and regulate its subcellular localisation and function.

5/7/19
DIALOG(R)File 5:Biosis Previews(R)

0014404717 BIOSIS NO.: 200300363436
%%%Parkin%%% facilitates the elimination of expanded polyglutamine proteins and leads to preservation of proteasome function.
AUTHOR: Tsai Yien Che; Fishman Paul S; Thakor Nitish V; Oyler George A (Reprint)
AUTHOR ADDRESS: Dept. of Neurology, 10 North Greene St., Baltimore, MD, 21201, USA**USA
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JOURNAL: Journal of Biological Chemistry 278 (24): p22044-22055 June 13, 2003 2003
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Parkin%%%, the most commonly mutated gene in familial Parkinson's disease, encodes an E3 ubiquitin ligase. A number of candidate substrates have been identified for %%%parkin%%% ubiquitin ligase action including CDCrel-1, o-glycosylated alpha-synuclein, Pael-R, and synphilin-1. We now show that %%%parkin%%% promotes the ubiquitination and degradation of an expanded polyglutamine protein. Overexpression of %%%parkin%%% reduces aggregation and cytotoxicity of an expanded polyglutamine ataxin-3 fragment. Using a cellular proteasome

indicator system based on a destabilized form of green fluorescent protein, we demonstrate that %%%parkin%%% reduces proteasome impairment and caspase-12 activation induced by an expanded polyglutamine protein. %%%Parkin%%% forms a complex with the expanded polyglutamine protein, heat shock protein 70 (Hsp70) and the proteasome, which may be important for the elimination of the expanded polyglutamine protein. Hsp70 enhances %%%parkin%%% %%%binding%%% and ubiquitination of expanded polyglutamine protein in vitro suggesting that Hsp70 may help to recruit misfolded proteins as substrates for %%%parkin%%% E3 ubiquitin ligase activity. We speculate that %%%parkin%%% may function to relieve endoplasmic reticulum stress by preserving proteasome activity in the presence of misfolded proteins. Loss of %%%parkin%%% function and the resulting proteasomal impairment may contribute to the accumulation of toxic aberrant proteins in neurodegenerative diseases including Parkinson's disease.

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DIALOG(R)File 5:Biosis Previews(R)

0014381216 BIOSIS NO.: 200300337959
%%%Parkin%%% binds the Rpn10 subunit of 26S proteasomes through its ubiquitin-like domain.
AUTHOR: Sakata Eri; Yamaguchi Yoshiki; Kurimoto Eiji; Kikuchi Jun; Yokoyama Shigeyuki; Yamada Shingo; Kawahara Hiroyuki; Yokosawa Hideyoshi; Hattori Nobutaka; Mizuno Yoshikuni; Tanaka Keiji; Kato Koichi (Reprint)
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JOURNAL: EMBO Reports 4 (3): p301-306 March 2003 2003
MEDIUM: print
ISSN: 1469-221X _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Parkin%%%, a product of the causative gene of autosomal-recessive juvenile parkinsonism (AR-JP), is a RING-type E3 ubiquitin ligase and has an amino-terminal ubiquitin-like (Ubl) domain. Although a single mutation that causes an Arg to Pro substitution at position 42 of the Ubl domain (the Arg 42 mutation) has been identified in AR-JP patients, the function of this domain is not clear. In this study, we determined the three-dimensional structure of the Ubl domain of %%%parkin%%% by NMR, in particular by extensive use of backbone 15N-1H residual dipolar-coupling data. Inspection of chemical-shift-perturbation data showed that the %%%parkin%%% Ubl domain binds the Rpn10 subunit of 26S proteasomes via the region of %%%parkin%%% that includes position 42. Our findings suggest that the Arg 42 mutation induces a conformational change in the Rpn10-%%%binding%%% site of Ubl, resulting in impaired proteasomal %%%binding%%% of %%%parkin%%%, which could be the cause of AR-JP.

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DIALOG(R)File 5:Biosis Previews(R)

0014347330 BIOSIS NO.: 200300304819
%%%PARKIN%%% BINDS TO alpha/beta TUBULIN HETERODIMERS AND ENHANCES THEIR UBIQUITINATION.
AUTHOR: Ren Y (Reprint); Zhao J (Reprint); Feng J (Reprint)
AUTHOR ADDRESS: Physiology and Biophysics, SUNY-Buffalo, Buffalo, NY, USA** USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 484.15 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Through yeast two-hybrid screening, we previously identified MAP1A as a %%%binding%%% protein for %%%parkin%%%. However, the interaction was relatively weak. In Taxol-mediated microtubule co-assembly assays, we found that %%%parkin%%% bound to microtubules very tightly. The %%%binding%%% could not be disrupted in high salt conditions that dissociate MAP1A and MAP2 from microtubules. In rat brain homogenates, alpha/beta tubulins were co-immunoprecipitated with %%%parkin%%% antibody at 4C and in the presence of colchicine, a condition where tubulins exit as alpha/beta heterodimers. These lines of evidence indicate that %%%parkin%%% binds to alpha/beta tubulin heterodimers as well as polymerized microtubules. In cultured neurons, glials, cell lines and rat brain sections, %%%parkin%%% exhibited punctated immunostaining along microtubules, with very high degree of co-localization. This staining pattern did not coincide with those of postsynaptic densities (using PSD95 as a marker) or presynaptic terminals (using synaptophysin as a marker). When %%%parkin%%% and HA-tagged ubiquitin were co-transfected into HEK293 cells, the ubiquitination of endogenous alpha-and beta-tubulins was significantly increased. Further enhancement was observed when cells were treated with lactacystin. Taken together, these results show that %%%parkin%%% is a tubulin-%%%binding%%% protein that may play an important role in the ubiquitination and degradation of misfolded tubulins, as the correct folding of tubulin alpha/beta heterodimers requires the coordinated actions of a series of chaperons and co-factors, which may nevertheless produce small amount of misfolded tubulins due to the complexity and reversibility of the process.

5/7/22
DIALOG(R)File 5:Biosis Previews(R)

0014347329 BIOSIS NO.: 200300304818
%%%PARKIN%%% IS RECRUITED TO THE CENTROSOME IN RESPONSE TO ACCUMULATION OF MISFOLDED PROTEINS.
AUTHOR: Zhao J (Reprint); Ren Y (Reprint); Feng J (Reprint)
AUTHOR ADDRESS: Dept. of Physiology and Biophysics, SUNY-Buffalo, Buffalo, NY, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 484.14 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: It has been shown that %%%parkin%%% suppresses cell death induced by unfolded protein stress, presumably through its ability to ubiquitinate misfolded proteins to increase their degradation. In the cell, accumulation of misfolded proteins leads to their aggregation in the centrosome, most likely by active transport processes along microtubules, whose minus ends are anchored on gamma-tubulins in the centrosome. Here we report that %%%parkin%%% was accumulated in the centrosome in response to lactacystin treatment. This effect was dependent on the concentration and duration of the treatment. The underlying mechanism for this phenomenon is the %%%binding%%% between %%%parkin%%% and gamma-tubulin, as evidenced by their co-immunoprecipitation in transfected 293 cells and rat brain homogenates. Furthermore, we found that %%%parkin%%% enhanced the ubiquitination of gamma-tubulins, especially in the presence of lactacystin. Correspondingly, ubiquitin staining was markedly increased in the centrosome when the cells were treated with lactacystin. Taken together, these data indicate that in response to aggregation of misfolded proteins in the centrosome, %%%parkin%%% may be recruited there, through its ability to bind gamma-tubulins, to enhance the ubiquitination and degradation of misfolded proteins, as well as

gamma-tubulins. The results suggest that %%%parkin%%%-mediated protein ubiquitination and degradation may occur in a specific subcellular locale, rather than diffusely in the cytosol. The recruitment of %%%parkin%%% to the centrosome may provide a mechanism by which cells ubiquitinate and degrade large amount of protein aggregates to suppress unfolded protein stress.

5/7/23
DIALOG(R)File 5:Biosis Previews(R)

0014347318 BIOSIS NO.: 200300304807
%%%PARKIN%%% INTERACTS WITH THE PROTEASOME.
AUTHOR: Fallon L (Reprint); Moreau F (Reprint); Haber M (Reprint); Fon E A (Reprint)
AUTHOR ADDRESS: Neurology and Neurosurgery, Montreal Neurological Institute, McGill University, Montreal, PQ, Canada**Canada
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 484.2 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Parkinsons disease (PD) involves the selective degeneration of midbrain dopamine neurons, resulting in motor abnormalities and progressive disability but the underlying cause remains unknown. Mutations in the %%%parkin%%% gene cause an autosomal recessive form of PD that account for more cases than all the other genetic causes combined. %%%Parkin%%% functions in the ubiquitin (Ub) proteasome pathway, as an E3 Ub-ligase, mediating the E2-dependent transfer of Ub onto substrate proteins. Ubiquitinated proteins are then recognized and degraded by the 26S proteasome, a large multimeric proteolytic complex. Interestingly, the N-terminus of %%%parkin%%% encodes a Ub-like domain (Ubl), which has been shown in other proteins, such as RAD23 and PLIC, to bind the proteasome. Using GST-Ubl pull-downs from HEK293 cells and brain lysates, we show here that the %%%parkin%%% Ubl also binds the proteasome. Further, we show that %%%parkin%%% co-immunoprecipitates with proteasome in brain fractions, indicating that they interact in vivo. Importantly, we find that in brain synaptic fractions, the %%%parkin%%% -proteasome interaction occurs predominantly in a membrane compartment. We have shown previously that %%%parkin%%% is localized to the postsynaptic density where it associates with a large multimeric protein complex implicated in NMDA receptor signaling, possibly via its extreme C-terminus, which encodes a PDZ-%%%binding%%% motif that is selectively truncated by a PD-causing mutation (Fallon et al. 2002 JBC 277:486). We report here that this synaptic complex also contains proteasome, suggesting that the %%%parkin%%% Ubl could target the proteasome to the synapse and thereby physically couple %%%parkin%%%-mediated ubiquitination with proteasome-mediated degradation.

5/7/24
DIALOG(R)File 5:Biosis Previews(R)

0014315191 BIOSIS NO.: 200300269724
GLYCINE RECEPTOR INTERACTING PROTEINS.
AUTHOR: Harvey R J (Reprint); Harvey K (Reprint); Duguid I C (Reprint); Pearce B R (Reprint); White J H; Smart T G (Reprint)
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JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 138.2 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102

SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The differential interaction of intracellular proteins with embryonic and adult glycine receptor (GlyR) isoforms may play a crucial role in the selective construction and maintenance of glycinergic synapses. To assess whether GlyR interacting proteins apart from gephyrin exist, we used the GAL4 yeast two-hybrid system (YTH), a reliable method for assessing protein-protein interactions. We performed a YTH screen for the GlyR alpha3 subunit, using the large intracellular M3-M4 domain as bait, in conjunction with an adult human brain cDNA library. Over 100 'hits' were characterised, representing cDNAs encoding portions of three known proteins: importin alpha3, importin alpha4 and synphilin-1. In specificity tests, we found that both importin alpha subunits and synphilin-1 also interacted with a GlyR alpha1 subunit bait, but not baits for the GlyR alpha2 or beta subunits. Characterisation of the %%%binding%%% sites for these interactors on the GlyR alpha3 subunit intracellular loop revealed that the importins and synphilin-1 bind to separate domains. We propose that importin alpha subunits (which facilitate the transport of proteins into the nucleus) may use GlyRs as 'docking points' at synapses for collecting signalling molecules such as transcription factors. In contrast, the large cytoplasmic protein synphilin-1, which interacts with both alpha-synuclein and the E3 ubiquitin-protein ligase %%%Parkin%%%, has been implicated in the pathogenesis of Parkinson's disease. We will present lines of evidence supporting a role for adult GlyR isoforms in cell death and Lewy body formation.

5/7/25
DIALOG(R)File 5:Biosis Previews(R)

0014314899 BIOSIS NO.: 200300269432
INTERACTION BETWEEN %%%PARKIN%%% AND GLYCOSYLATED alpha - SYNUCLEIN.
AUTHOR: Shimura H (Reprint); Schlossmacher M (Reprint); Rasakham S (Reprint); Hattori N; Mizuno Y; Kosik K (Reprint); Selkoe D (Reprint)
AUTHOR ADDRESS: Department of Neurology, Center for Neurologic Diseases, Harvard Medical School, Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 118.6 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the %%%parkin%%% gene have been identified in autosomal recessive Parkinson's disease (ARPD), and %%%parkin%%% acts as an ubiquitin (Ub) ligase. Two mutations in the alpha-synuclein (alphaS) gene (A53T and A30P) cause rare forms of autosomal dominant PD. Because alphaS is a major constituent of Lewy bodies, the pathological hallmark of PD, we examined whether %%%parkin%%% plays a role in alphaS metabolism and in the pathogenesis of PD. We recently identified a protein complex in normal human brain that includes %%%parkin%%% as an E3 Ub ligase, UbcH7 as its associated E2, and a novel 22 kDa O-glycosylated isoform of alphaS (alphaSp22) as a substrate. alphaSp22 was further modified by normal but not mutant %%%parkin%%% into high Mr polyubiquitinated species in vitro. We now demonstrate that deglycosylation of alphaSp22 with sialidase or sialidase and O-glycosidase prevents the %%%binding%%% of myc-%%%parkin%%% to deglycosylated alphaSp16 in vitro. In addition, we have identified a specific lectin that binds alphaSp22 and have developed a 4-step purification protocol to obtain completely purified alphaSp22, based on silver gels. We conclude that: (1) alphaSp22 is a substrate for parkins Ub ligase activity from human brain, (2) loss of function in %%%parkin%%%-deficient ARPD causes alphaSp22 accumulation, (3) alphaSp22 can be purified from human brain by NH4SO4 precipitation, lectin

chromatography and two anti-alphaS antibody affinity columns, (4) the interaction of wild type %%%parkin%%% with alphaSp22 depends on intact sugar groups on the glycoprotein and (5) alphaSp22 can form oligomers in vitro. These findings support the hypothesis that alphaSp22 may play an important role in idiopathic PD as well as ARPD.

5/7/26
DIALOG(R)File 5:Biosis Previews(R)

0014314896 BIOSIS NO.: 200300269429
POSSIBLE INVOLVEMENT OF A SEPTIN IN THE ETIOLOGY OF PARKINSON'S DISEASE AND OTHER SYNUCLEINOPATHIES.
AUTHOR: Kinoshita M (Reprint); Ihara M; Tomimoto H; Kitayama H; Akiguchi I; McLean P J; Shibasaki H; Noda M
AUTHOR ADDRESS: Department of Cell Biology, Harvard Medical School, Boston, MA, USA**USA
JOURNAL: Society for Neuroscience Abstract Viewer and Itinerary Planner 2002 pAbstract No. 118.3 2002 2002
MEDIUM: cd-rom
CONFERENCE/MEETING: 32nd Annual Meeting of the Society for Neuroscience Orlando, Florida, USA November 02-07, 2002; 20021102
SPONSOR: Society for Neuroscience
DOCUMENT TYPE: Meeting; Meeting Poster; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Septins are GTP-%%%binding%%% proteins which form filamentous complexes and play roles in cytokinesis and exocytosis. Some septins are implicated in neurodegenerative disorders: the presence of a few septins in neurofibrillary tangles in Alzheimer's disease; ubiquitination of a septin by %%%parkin%%%; and involvement of a septin-like protein in TGFbeta-mediated apoptosis. Our immunohistochemical screening revealed consistent presence of a septin, but not five other septins, in the majority of alpha-synuclein-positive cytoplasmic inclusions in postmortem human brains with Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy. This septin and alpha-synuclein were co-immunoprecipitable from normal human brain lysates, suggestive of physiological interaction of the two proteins. When co-expressed in cultured cells, the septin and alpha-synuclein formed detergent-insoluble complexes. Proteasomal inhibition on these cells induced formation of cytoplasmic aggregates and Lewy body-like inclusions containing ubiquitinated septin and alpha-synuclein. Interestingly, the septin and alpha-synuclein synergistically accelerated cell death induced by proteasomal inhibition. These findings suggest an active role of the septin in the alpha-synuclein-associated neurodegenerative disorders or synucleinopathies.

5/7/27
DIALOG(R)File 5:Biosis Previews(R)

0014312454 BIOSIS NO.: 200300266987
%%%Parkin%%% binds to alpha/beta tubulin and increases their ubiquitination and degradation.
AUTHOR: Ren Yong; Zhao Jinghui; Feng Jian (Reprint)
AUTHOR ADDRESS: Department of Physiology and Biophysics, State University of New York at Buffalo, 124 Sherman Hall, Buffalo, NY, 14214, USA**USA
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JOURNAL: Journal of Neuroscience 23 (8): p3316-3324 April 15, 2003 2003
MEDIUM: print
ISSN: 0270-6474 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In addition to inhibiting the mitochondrial respiratory chain, toxins known to cause Parkinson's disease (PD), such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rotenone, also strongly

depolymerize microtubules and increase tubulin degradation. Microtubules are polymers of tubulin alpha/beta heterodimers, whose correct folding requires coordinated actions of cellular chaperonins and cofactors. Misfolded tubulin monomers are highly toxic and quickly degraded through a hitherto unknown mechanism. Here we report that %%%parkin%%%, a protein-ubiquitin E3 ligase linked to PD, was tightly bound to microtubules in taxol-mediated microtubule coassembly assays. In lysates from the rat brain or transfected human embryonic kidney (HEK) 293 cells, alpha-tubulin and beta-tubulin were strongly coimmunoprecipitated with %%%parkin%%% at 4degreeC in the presence of colchicine, a condition in which tubulin exits as alpha/beta heterodimers. At the subcellular level, %%%parkin%%% exhibited punctate immunostaining along microtubules in rat brain sections, cultured primary neurons, glial cells, and cell lines. This pattern of subcellular localization was abolished in cells treated with the microtubule-depolymerizing drug colchicine. The %%%binding%%% between %%%parkin%%% and tubulin apparently led to increased ubiquitination and accelerated degradation of alpha- and beta-tubulins in HEK293 cells. Similarly ubiquitinated tubulins were also observed in rat brain lysates. Furthermore, %%%parkin%%% mutants found in PD patients did not ubiquitinate or degrade either tubulin. Taken together, our results show that %%%parkin%%% is a novel tubulin-%%%binding%%% protein, as well as a microtubule-associated protein. Its ability to enhance the ubiquitination and degradation of misfolded tubulins may play a significant role in protecting neurons from toxins that cause PD.

0014193429 BIOSIS NO.: 200300152148
Identification of a novel gene linked to %%%parkin%%% via a bi-directional promoter.
AUTHOR: West Andrew B; Lockhart Paul J; O'Farell Casey; Farrer Matthew J (Reprint)
AUTHOR ADDRESS: Laboratories of Neurogenetics Department of Neuroscience and Neurology, Mayo Clinic Jacksonville, 1500 San Pablo Road, Birdsall Building, Jacksonville, FL, 32224, USA**USA
AUTHOR E-MAIL ADDRESS: farrer.matthew@mayo.edu
JOURNAL: Journal of Molecular Biology 326 (1): p11-19 7 February 2003 2003
MEDIUM: print
ISSN: 0022-2836 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations of the %%%parkin%%% gene on chromosome 6q25-27 are the predominant genetic cause of early-onset and autosomal recessive juvenile parkinsonism. %%%Parkin%%% is a multi-domain protein with ubiquitin-protein E3 ligase activity that has a role in the proteasome-mediated degradation of target substrates. Although the %%%parkin%%% gene contains an expanded intron/exon structure and spans more than 1.3 Mb, we have identified a novel transcript that initiates 204 bp upstream of %%%parkin%%% and spans over 0.6 Mb, antisense to %%%parkin%%%. We have tentatively named this novel gene %%%Parkin%%% co-regulated gene, or PACRG. A 35 bp site of bi-directional transcription activation within the common promoter was mapped using dual-luciferase assays. This region appeared to be responsible for the majority of transcription regulation of both genes, and comparison of the mouse and human sequences revealed conserved transcription factor-%%%binding%%% sites. A 15 bp interval within the activation region, containing a non-canonical myc-%%%binding%%% site, bound nuclear protein derived from human substantia nigra. Database analysis identified highly conserved homologs of PACRG encoded by the mouse and Drosophila genomes, and Northern analysis demonstrated that PACRG and %%%parkin%%% were co-expressed in many tissues, including brain, heart and muscle. Western analysis revealed a protein of the predicted size, approximately 30 kDa, which was expressed in mouse and human brain. Although PACRG protein lacks known functional domains, in silico prediction suggests a potential link to the ubiquitin/proteasome system.

5/7/29
DIALOG(R)File 5:Biosis Previews(R)

0014132940 BIOSIS NO.: 200300091659
Comparative genomics of the RBR family, including the Parkinson's disease-related gene %%%parkin%%% and the genes of the ariadne subfamily.
AUTHOR: Marin Ignacio (Reprint); Ferrus Alberto
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JOURNAL: Molecular Biology and Evolution 19 (12): p2039-2050 December 2002 2002
MEDIUM: print
ISSN: 0737-4038
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Genes of the RBR family are characterized by the RBR signature (two RING finger domains separated by an IBR/DRIL domain). The RBR family is widespread in eukaryotes, with numerous members in animals (mammals, Drosophila, Caenorhabditis) and plants (Arabidopsis). But yeasts, such as Saccharomyces cerevisiae or Schizosaccharomyces pombe, contain only two RBR genes. We determined the phylogenetic relationships and the most likely orthologs in different species of several family members for which functional data are available. These include: (1) %%%parkin%%%, whose mutations are involved in forms of familial Parkinson's disease; (2) the ariadne genes, recently characterized in Drosophila and mammals; (3) XYbp and Dorfin, two mammalian genes whose products interact with the centrosome; (4) XAP3, RBCKJ, and UIP28, mammalian genes encoding Protein Kinase-C-%%%binding%%% proteins; and (5) ARA54, an androgen receptor coactivator. Because several of these genes are involved in ubiquitination, we used phylogenetic and structural analyses to explore the hypothesis that all RBR proteins might play a role in ubiquitination. We show that the involvement of RBR proteins in ubiquitination predates the animals-plants-fungi divergence. On the basis of the evidence provided by cases of gene fusion, we suggest that Ariadne proteins interact with cullin domain-containing proteins to form complexes with ubiquitin-ligase activity.

5/7/30
DIALOG(R)File 5:Biosis Previews(R)

0014113538 BIOSIS NO.: 200300072257
Astrocytic but not neuronal increased expression and redistribution of %%%parkin%%% during unfolded protein stress.
AUTHOR: Ledesma Maria Dolores; Galvan Cristian; Hellias Bianca; Dotti Carlos; Jensen Poul Henning (Reprint)
AUTHOR ADDRESS: Department of Medical Biochemistry, University of Aarhus, Bldg 170, DK-8000, Aarhus C, Denmark**Denmark
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JOURNAL: Journal of Neurochemistry 83 (6): p1431-1440 December 2002 2002
MEDIUM: print
ISSN: 0022-3042
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Parkin%%% is a ubiquitin ligase that facilitates proteasomal protein degradation and is involved in a common autosomal recessive form of Parkinson's disease. Its expression is part of the unfolded protein response in cell lines where its overexpression protects against unfolded protein stress. How %%%parkin%%% expression is regulated in brain primary cells under stress situations is however, less well established. Here, the cellular and subcellular localization of %%%parkin%%% under basal conditions and during unfolded protein stress was investigated in primary cultures of rat astrocytes and hippocampal neurons. Immunofluorescence

microscopy and biochemical analysis demonstrated that %%%parkin%%% is mainly associated with the endoplasmic reticulum (ER) in hippocampal neurons while it is associated with Golgi membranes, the nuclei and light vesicles in astrocytes. The constitutive %%%parkin%%% expression was high in neurons as compared with astrocytes. However, unfolded protein stress elicited a selective increase in astrocytic %%%parkin%%% expression and a change in distribution, whereas neuronal %%%parkin%%% remained largely unmodified. The cell specific differences argue in favour of different cellular %%%binding%%% sites and substrates for the protein and a pathogenic role for astrocytes in Parkinson's disease caused by %%%parkin%%% dysfunction.

5/7/31
DIALOG(R)File 5:Biosis Previews(R)

0014067152 BIOSIS NO.: 200300025871
Striatal dopaminergic denervation in early and late onset Parkinson's disease assessed by PET and the tracer (11C)FECIT: Preliminary findings in one patient with autosomal recessive parkinsonism (Park2).
AUTHOR: Antonini A (Reprint); Moresco R M; Gobbo C; De Notaris R; Panzacchi A; Barone P; Bonifati V; Pezzoli G; Fazio F
AUTHOR ADDRESS: Parkinson Center, Department of Neurosciences, Istituti Clinici di Perfezionamento, Milan, Italy**Italy
JOURNAL: Neurological Sciences 23 (Supplement 2): pS51-S52 September 2002 2002
MEDIUM: print
ISSN: 1590-1874 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Neuroimaging studies of striatal dopamine transporters (DAT) have shown that this measurement is a specific marker of dopaminergic degeneration in patients with Parkinson's disease. However, little data is available in subjects with early disease onset, particularly in those with autosomal recessive parkinsonism. We measured striatal DAT %%%binding%%% in 10 patients with early onset PD (onset <40 years) and in 10 with late onset PD (onset >50 years) using PET and the tracer (11C)FECIT. One early onset subject presented a mutation in the %%%parkin%%% gene consistent with autosomal recessive parkinsonism. Data were compared with those of 15 control subjects. We found a comparable decrement of striatal DAT %%%binding%%% in early and late onset PD. Loss was widespread and bilateral in the patient carrying the Park2 mutation, suggesting a different pattern of denervation in these individuals.

5/7/32
DIALOG(R)File 5:Biosis Previews(R)

0014050573 BIOSIS NO.: 200300009292
Identification of brain proteins that interact with 2-methylnorharman: An analog of the parkinsonian-inducing toxin, MPP+.
AUTHOR: Gearhart Debra A (Reprint); Toole Patricia F; Beach J Warren
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JOURNAL: Neuroscience Research 44 (3): p255-265 November 2002 2002
MEDIUM: print
ISSN: 0168-0102 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: N-Methylated beta-carbolines, including 2-methylnorharman, are structural and functional analogs of the parkinsonian-inducing toxin, MPP+. We are investigating N-methylated beta-carbolines, including 2-methylnorharman, as possible etiologic factors in the pathogenesis of Parkinson's disease. The cellular targets of N-methylated

beta-carboline-mediated cytotoxicity are unknown; therefore, we used the T7Select(R) Phage Display System in a novel approach to identify brain proteins that bind to 2-methylnorharman. We incubated (biopanned) immobilized 2-methylnorharman with a phage display cDNA library that expressed a library of human brain proteins on the surface of bacteriophage T7. We washed off unbound phage, amplified the phage that were bound to 2-methylnorharman, and enriched for toxin-interacting phage by repeating the biopanning and amplification steps. The cDNA sequences from the toxin-interacting phage were used to derive the amino acid sequences of the phage-displayed proteins. Five of the six 2-methylnorharman-interacting proteins may have relevance to Parkinson's disease: alpha-tubulin, paraoxonase, dorfin, fatty acid %%%binding%%% protein, and platelet-activating factor acetylhydrolase. Dorfin has sequence homology with %%%parkin%%%, which is interesting because mutations in the %%%parkin%%% gene associate with early-onset Parkinson's disease. Our findings are the basis for future studies aimed at determining whether 2-methylnorharman affects the function of these specific proteins in vitro and in vivo.

5/7/33
DIALOG(R)File 5:Biosis Previews(R)

0013960549 BIOSIS NO.: 200200554060
Interaction of %%%parkin%%% with vesicle-associated proteins
AUTHOR: Huynh Duong P (Reprint); Dy Maria (Reprint); Nguyen Dung (Reprint); Pulst Stefan M (Reprint)
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JOURNAL: Neurology 58 (7 Supplement 3): pA410 April 9, 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 54th Annual Meeting of the American Academy of Neurology Denver, Colorado, USA April 13-20, 2002; 20020413
ISSN: 0028-3878
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RECORD TYPE: Citation
LANGUAGE: English

5/7/34
DIALOG(R)File 5:Biosis Previews(R)

0013716857 BIOSIS NO.: 200200310368
%%%Parkin%%% localizes to the Lewy bodies of Parkinson disease and dementia with Lewy bodies
AUTHOR: Schlossmacher Michael G (Reprint); Frosch Matthew P; Gai Wei Ping; Medina Miguel; Sharma Nutan; Forno Lysia; Ochiishi Tomoyo; Shimura Hideki ; Sharon Ronit; Hattori Nobutaka; Langston J William; Mizuno Yoshikuni; Hyman Bradley T; Selkoe Dennis J; Kosik Kenneth S
AUTHOR ADDRESS: Center for Neurologic Diseases, Brigham and Women's Hospital, 77 Ave. Louis Pasteur, Boston, MA, 02115, USA**USA
JOURNAL: American Journal of Pathology 160 (5): p1655-1667 May, 2002 2002
MEDIUM: print
ISSN: 0002-9440
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in alpha-synuclein (alphaS) and %%%parkin%%% cause heritable forms of Parkinson disease (PD). We hypothesized that neuronal %%%parkin%%%, a known E3 ubiquitin ligase, facilitates the formation of Lewy bodies (LBs), a pathological hallmark of PD. Here, we report that affinity-purified %%%parkin%%% antibodies labeled classical LBs in substantia nigra sections from four related human disorders: sporadic PD, inherited alphaS-linked PD, dementia with LBs (DLB), and LB-positive, %%%parkin%%%-linked PD. Anti-%%%parkin%%% antibodies also detected LBs in entorhinal and cingulate cortices from DLB brain and alphaS inclusions in sympathetic gangliocytes from sporadic PD. Double labeling with confocal microscopy of DLB midbrain sections revealed that apprx90% of anti-alphaS-reactive LBs were also detected by a %%%parkin%%% antibody to

amino acids 342 to 353. Accordingly, %%%parkin%%% proteins, including the 53-kd mature isoform, were present in affinity-isolated LBs from DLB cortex. Fluorescence resonance energy transfer and immunoelectron microscopy showed that alphaS and %%%parkin%%% co-localized within brainstem and cortical LBs. Biochemically, %%%parkin%%% appeared most enriched in cytosolic and postsynaptic fractions of adult rat brain, but also in purified, alphaS-rich presynaptic elements that additionally contained %%%parkin%%%'s E2-%%%binding%%% partner, UbcH7. We conclude that %%%parkin%%% and UbcH7 are present with alphaS in subcellular compartments of normal brain and that %%%parkin%%% frequently co-localizes with alphaS aggregates in the characteristic LB inclusions of PD and DLB. These results suggest that functional %%%parkin%%% proteins may be required during LB formation.

5/7/35
DIALOG(R)File 5:Biosis Previews(R)

0013661823 BIOSIS NO.: 200200255334
A double RING-H2 domain in RNF32, a gene expressed during sperm formation
AUTHOR: van Baren Marijke J (Reprint); van der Linde Herma C; Breedveld Guido J; Baarends Willy M; Rizzu Patrizia; de Graaff Esther; Oostra Ben A ; Heutink Peter
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JOURNAL: Biochemical and Biophysical Research Communications 292 (1): p 58-65 March 22, 2002 2002
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The RING domain is a cysteine-rich zinc-%%%binding%%% motif, which is found in a wide variety of proteins, among which are several proto-oncogenes and the gene implicated in autosomal recessive juvenile parkinsonism, %%%Parkin%%%. The domain mediates %%%binding%%% to other proteins, either via their RING domains or other motifs. In several proteins, RING domains are found in combination with other cysteine-rich %%%binding%%% motifs and some proteins contain two RING domains. Recent evidence suggests that RING finger proteins function in the ubiquitin pathway as E3 ligases. A variant of the RING domain is the RING-H2 domain, in which one of the cysteine is replaced by a histidine. We have cloned and characterized a novel gene, RNF32, located on chromosome 7q36. RNF32 is contained in 37 kb of genomic DNA and consists of 9 constitutive and 8 alternatively spliced exons, most of which are alternative first exons. A long and a short transcript of the gene are expressed; the short transcript containing exons 1-4 only. This gene encodes two RING-H2 domains separated by an IQ domain of unknown function. This is the first reported gene with a double RING-H2 domain. In humans, RNF32 overlaps with a processed retroposon located on the opposite strand, C7orf13. RNF32 is specifically expressed in testis and ovary, whereas C7orf13 is testis-specific, suggesting that its expression may be regulated by elements in the RNF32 promoter region. RNF32 is expressed during spermatogenesis, most likely in spermatocytes and/or in spermatids, suggesting a possible role in sperm formation.

5/7/36
DIALOG(R)File 5:Biosis Previews(R)

0013651519 BIOSIS NO.: 200200245030
%%%Parkin%%% mutations in a patient with hemiparkinsonism-hemiatrophy: A clinical-genetic and PET study
AUTHOR: Pramstaller P P (Reprint); Kunig G; Leenders K; Kann M; Hedrich K; Vieregge P; Goetz C G; Klein C
AUTHOR ADDRESS: Department of Neurology, Regional General Hospital, Bolzano/Bozen, 5 Lorenz Boehler, I-39100, Bolzano, Italy**Italy
JOURNAL: Neurology 58 (5): p808-810 March 12, 2002 2002

MEDIUM: print
ISSN: 0028-3878
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The authors describe a 37-year-old woman with early-onset hemiparkinsonism (HP) and ipsilateral body hemiatrophy (HA). Genetic analysis revealed a missense mutation (Arg275Trp) and a duplication of exon 7 of %%%parkin%%%. The complementary metabolic and receptor pattern of PET ligands corresponded to that typically found in idiopathic PD, although tracer %%%binding%%% asymmetry was lacking. %%%Parkin%%% mutations should be considered in HPHA, particularly when there is a younger age at onset and dystonia is an early sign.

5/7/37
DIALOG(R)File 5:Biosis Previews(R)

0013525145 BIOSIS NO.: 200200118656
%%%Parkin%%% and CASK/LIN-2 associate via a PDZ-mediated interaction and are co-localized in lipid rafts and postsynaptic densities in brain
AUTHOR: Fallon Lara; Moreau France; Croft Benjamin G; Labib Noura; Gu Wen-Jie; Fon Edward A (Reprint)
AUTHOR ADDRESS: Center for Neuronal Survival, Montreal Neurological Inst., McGill University, 3801 University St., Montreal, PQ, H3A 2B4, Canada** Canada
JOURNAL: Journal of Biological Chemistry 277 (1): p486-491 January 4, 2002
2002
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the gene encoding %%%parkin%%% cause an autosomal recessive juvenile-onset form of Parkinson's disease. %%%Parkin%%% functions as a RING-type E3 ubiquitin-ligase, coordinating the transfer of ubiquitin to substrate proteins and thereby targeting them for degradation by the proteasome. We now report that the extreme C terminus of %%%parkin%%%, which is selectively truncated by a Parkinson's disease-causing mutation, functions as a class II PDZ-%%%binding%%% motif that binds CASK, the mammalian homolog of Caenorhabditis elegans Lin-2, but not other PDZ proteins in brain extracts. Importantly, %%%parkin%%% co-localizes with CASK at synapses in cultured cortical neurons as well as in postsynaptic densities and lipid rafts in brain. Further, %%%parkin%%% associates not only with CASK but also with other postsynaptic proteins in the N-methyl D-aspartate (NMDA) receptor-signaling complex, in rat brain in vivo. Finally, despite exhibiting E2-dependent ubiquitin ligase activity, rat brain %%%parkin%%% does not ubiquitinate CASK, suggesting that CASK may function in targeting or scaffolding %%%parkin%%% within the postsynaptic complex rather than as a direct substrate for %%%parkin%%%-mediated ubiquitination. These data implicate for the first time a PDZ-mediated interaction between %%%parkin%%% and CASK in neurodegeneration and possibly in ubiquitination of proteins involved in synaptic transmission and plasticity.

5/7/38
DIALOG(R)File 5:Biosis Previews(R)

0013416026 BIOSIS NO.: 200200009537
Identification of molecular determinants required for interaction of ubiquitin-conjugating enzymes and RING finger proteins
AUTHOR: Martinez-Noel Gustavo; Mueller Ursula; Harbers Klaus (Reprint)
AUTHOR ADDRESS: Heinrich-Pette-Institut fuer Experimentelle Virologie und Immunologie an der Universitaet Hamburg, Martinistr.52, D-2025, Hamburg, Germany**Germany

JOURNAL: European Journal of Biochemistry 268 (22): p5912-5919 November, 2001 2001
MEDIUM: print
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recent results from several laboratories suggest that the interaction of E2 ubiquitin-conjugating enzymes with the RING finger domain has a central role in mediating the transfer of ubiquitin to proteins. Here we present a mutational analysis of the interaction between the E2 enzyme UbcM4/UbcH7 and three different RING finger proteins, termed UIPs, which, like %%%Parkin%%%, contain a RING1-IBR-RING2 motif. The results show that the E2 enzyme binds to the RING1 domain but not to the other cysteine/histidine-rich domains of the RING1-IBR-RING2 motif. Three regions within the UbcM4 molecule are involved in this interaction: the H1 alpha helix, loop L1, connecting the third and fourth strand of the beta sheet, and loop L2, located between the fourth beta strand and the second alpha helix. Loop L2 plays an important role in determining the specificity of interaction. The effects of L2 mutations on UbcM4/UIP interaction are different for each UIP, indicating that RING finger domains can vary considerably in their structural requirements for %%%binding%%% to E2 enzymes. The result that single amino-acid changes can regulate %%%binding%%% of E2 enzymes to different RING finger proteins suggests a novel approach to experimentally manipulate proteolytic pathways mediated by RING finger proteins.

5/7/39
DIALOG(R)File 5:Biosis Previews(R)

0013337387 BIOSIS NO.: 200100509226
%%%Parkin%%% colocalizes with actin filaments and synaptic vesicles, and interacts with synaptotagmin XI
AUTHOR: Huynh D P (Reprint); Nguyen D (Reprint); Dy M (Reprint); Pulst S M (Reprint)
AUTHOR ADDRESS: Dept Med/Neurology, Cedars-Sinai Hosp/UCLA, Los Angeles, CA, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p607 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Introduction: Inactivating mutations of the gene encoding %%%parkin%%% are responsible for autosomal recessive juvenile parkinsonism (AR-JP). However, little information on the function of %%%parkin%%% is known. Methods: Toward the elucidation of the function of %%%parkin%%%, we utilized immunofluorescent confocal microscopy to determine the subcellular distribution of %%%parkin%%% in cultured neurons and kidney cell. We used the yeast-two hybrid screening to identify proteins that interact with %%%parkin%%%. To confirm the yeast-two hybrid interaction, we utilized in-vitro %%%binding%%% and co-ip assays, followed by immunofluorescent confocal analyses to investigate the relative position of the interacting protein to %%%parkin%%%. Results: Confocal analyses and subcellular fractionation methods using specific %%%parkin%%% antibodies indicated that %%%parkin%%% colocalized with actin filament in kidney cells and synaptic vesicles in PC12 neurons. Yeast two-hybrid assays identified two cDNA clones that were further confirmed by co-immunoprecipitation and in vitro %%%binding%%% assays. Subsequent nucleotide analysis showed that one of the interacting proteins was the human synaptotagmin XI. The implication of %%%parkin%%% interaction with synaptotagmin XI is being investigated. Discussion: These results suggest that %%%parkin%%% may be involved in regulating the trafficking of synaptic vesicles via the cytoskeletal

system.

5/7/40
DIALOG(R)File 5:Biosis Previews(R)

0013320544 BIOSIS NO.: 200100492383
Identification of %%%parkin%%% interacting proteins
AUTHOR: Junn E (Reprint); Kim Y M (Reprint); Lee S S (Reprint); Lee G (Reprint); Mouradian M M (Reprint)
AUTHOR ADDRESS: GPU/ETB/NINDS, NIH, Bethesda, MD, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p516 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the gene coding for %%%parkin%%% cause an autosomal recessive form of Parkinson's disease. Recent reports indicate that %%%parkin%%% functions as an E3 ubiquitin ligase, and that Parkinson-causing mutations result in the inhibition of this activity. Therefore, it can speculated that deleterious accumulation of unknown substrate(s) may ensue the loss of %%%parkin%%% E3 activity in nigral neurons, ultimately leading to their degeneration. To identify %%%parkin%%% substrates, the yeast two hybrid screen was employed in search for its interacting partners. Since the ring finger domain activated basal transcription from the promoter in the reporter system, we used %%%parkin%%% fragment (1-167) devoid of the R1-IBR-R2 domain as bait. Approximately 6 million colonies were screened from a human adult brain cDNA library, and several candidate clones were selected. One of them was a CDCrel protein, a member of the septin family. Immunoprecipitation-immunoblot assays confirmed that these two proteins interact in 293T and COS-7 cells. This interaction does not require the ubiquitin-like domain of %%%parkin%%% which has previously been suggested to be important for substrate %%%binding%%%. Coexpression of %%%parkin%%% increased ubiquitinated CDCrel levels only slightly. Furthermore, kinetic studies of this CDCrel protein degradation in COS7 cells revealed no major difference in the presence of %%%parkin%%% overexpression compared with vector control. These observations suggest the possibility that this CDCrel may function as a regulatory partner of %%%parkin%%%, rather than primarily as its ubiquitin ligase substrate.

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DIALOG(R)File 5:Biosis Previews(R)

0013320542 BIOSIS NO.: 200100492381
Mutations in the %%%parkin%%% gene and %%%parkin%%% metabolism and function
AUTHOR: Petrucelli L (Reprint); Kehoe K (Reprint); Hernandez D (Reprint); Forno L; Cookson M (Reprint); Lockhart P (Reprint); Lincoln S (Reprint); Hardy J (Reprint); Langston W; Farrer M (Reprint)
AUTHOR ADDRESS: Neurogenetics, Mayo Clinic Jacksonville, Jacksonville, FL, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p515 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Autosomal recessive juvenile parkinsonism (AR-JP) is an early onset movement disorder, consisting of the triad of resting tremor, rigidity and bradykinesia. Patients are responsive to levodopa and show neuronal loss in the substantia nigra and locus ceruleus. Lewy body

pathology characteristic of PD is not associated with this disorder. AR-JP is caused by loss of function of the %%%parkin%%% gene, a ubiquitin protein ligase. We have identified two multigenerational American families with L-dopa responsive PD and early onset dystonia-parkinsonism. Sequence and haplotype analysis revealed a common chromosome 6 haplotype, containing a novel 40 bp exon 3 deletion that co-segregates with disease. In the proband of the smaller kindred, an exon 7 R275W substitution was also identified. Post mortem examination of the affected proband with these compound heterozygous mutations revealed Lewy body pathology. %%%Parkin%%% is auto-ubiquitinated which promotes its own degradation. The ring-finger domain within %%%parkin%%% is critical for %%%binding%%% of the E2 ubiquitinating conjugases. We report an increase in mutant %%%parkin%%% half-life and an accumulation of mutant %%%parkin%%% as a result of posttranslation modifications. Since this mutation lies in the ring-finger domain we investigated whether this mutation abolishes the E2 %%%binding%%% interface. We have determined whether mutant %%%parkin%%% binds to the E2 ubiquitinating conjugases. These data suggest that the loss of %%%parkin%%%'s ubiquitin-protein ligase activity, leading to accumulation of mutant protein, might be causal in familial autosomal recessive PD.

5/7/42
DIALOG(R)File 5:Biosis Previews(R)

0013320207 BIOSIS NO.: 200100492046
Structure-activity analysis of %%%Parkin%%% and interacting substrate proteins
AUTHOR: Rovelli G F (Reprint); Stauffer D (Reprint); Hartmann Y E (Reprint); Wiessner C (Reprint); Dev K K (Reprint)
AUTHOR ADDRESS: Nervous System, Novartis Pharma Research, Basel, Switzerland**Switzerland
JOURNAL: Society for Neuroscience Abstracts 27 (1): p517 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the %%%parkin%%% gene are a major cause of early-onset autosomal recessive Parkinson's disease. Patients carrying loss-of-function %%%parkin%%% mutations do not seem to develop Lewy bodies, the pathological hallmark of typical Parkinson's disease. Nevertheless, they have no specific clinical signs that distinguish them from patients with idiopathic Parkinson's disease. %%%Parkin%%% is 465 amino acids in length and contains an amino terminal ubiquitin homology domain (UHD), a central domain and a carboxy terminal RING1-IBR-RING2 domain. %%%Parkin%%% has been shown to function as an E3 ligase, which is defined as a factor that mediates poly-ubiquitination of specific substrates, marking them for degradation by the proteosome. %%%Parkin%%% loss-of-function mutations may cause a decrease in proteosomal clearance of specific cellular substrates that, upon accumulation, could lead to degeneration of dopaminergic neurons. We have undertaken a detailed structure-activity analysis of %%%Parkin%%% by over-expressing some of the truncating and missense mutations into dopaminergic MN9D and HEK293 cells; the effect of these mutations on cellular viability and neuritic extension was monitored by a reporter gene assay and immunofluorescence, respectively. A combination of yeast two-hybrid, ubiquitination and immunoprecipitation assays was then used to separate the E3 ligase property, i.e. facilitation of the E2-mediated ubiquitination, from the substrate %%%binding%%% properties of %%%Parkin%%%. We found that most of the %%%Parkin%%% mutants were characterised by low level of expression and did not significantly affect cellular viability.

5/7/43
DIALOG(R)File 5:Biosis Previews(R)

0013320206 BIOSIS NO.: 200100492045
%%%Parkin%%%-mediated ubiquitination and metabolism of hCDC-rel2A
AUTHOR: Choi P (Reprint); Petrucelli L; Chong M (Reprint); Bowser R; Cochran E; Lee J M (Reprint); Hardy J; Passer B; D'Adamio L; Wolozin B (Reprint)
AUTHOR ADDRESS: Pharmacology, Loyola Univ Chicago School of Medicine, Maywood, IL, USA**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1): p517 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001; 20011110
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in %%%parkin%%% are associated with various inherited forms of Parkinson's disease. %%%Parkin%%% is a ubiquitin ligase that catalyzes the attachment of ubiquitin moieties to protein substrates destined for proteasomal degradation. %%%Parkin%%% interacts with the ubiquitin conjugases UbcH7 and UbcH8 via its RING-IBR-RING domain. Substrate specificity is thought to be determined by %%%binding%%% to %%%parkin%%% at its amino terminal, which exhibits homology to ubiquitin. The substrates of %%%parkin%%%-mediated ubiquitination have not all been identified. To determine which proteins are ubiquitinated by %%%parkin%%% , we employed a yeast two-hybrid screen of a human brain cDNA library. The septin, human cell division control-related protein 2A (hCDC-rel2A), was isolated as a putative %%%parkin%%%-%%%binding%%% protein. The interaction between %%%parkin%%% and hCDC-rel2A was validated by their co-immunoprecipitation in human brain lysates. We also observed co-localization of %%%parkin%%% and hCDC-rel2A by immunofluorescent double labeling; both %%%parkin%%% and hCDC-rel2A were found to co-localize strongly in pigmented nigral neurons. Finally, %%%parkin%%% was shown to mediate ubiquitination and subsequent degradation of hCDC-rel2A. These findings, together with previous findings of %%%parkin%%%-mediated ubiquitination and degradation of a related septin, hCDC-rel1, suggest an important relationship between %%%parkin%%% and septins, and may lead to further elucidation of %%%parkin%%%'s normal and pathologic functions.

5/7/44
DIALOG(R)File 5:Biosis Previews(R)

0013267591 BIOSIS NO.: 200100439430
Bioinformatics applied to neurodegenerative diseases suggests physiological prion (PrP), Alzheimer's amyloid precursor (APP), Parkinson's %%%Parkin%%% (P) and Huntington's Huntingtin (H) proteins being (Cu/Zn)-metalloregulated RNA-%%%binding%%% protein families
AUTHOR: Wissler Josef H (Reprint); Logemann Enno
AUTHOR ADDRESS: IRD Biotechnology, ARCONS Applied Research, D-61231, Bad Nauheim, Germany**Germany
JOURNAL: Molecular Biology of the Cell 11 (Supplement): p132a Dec., 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 40th American Society for Cell Biology Annual Meeting San Francisco, CA, USA December 09-13, 2000; 20001209
SPONSOR: American Society for Cell Biology
ISSN: 1059-1524
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/7/45
DIALOG(R)File 5:Biosis Previews(R)

0013199534 BIOSIS NO.: 200100371373

Features of the %%%Parkin%%%/ariadne-like ubiquitin ligase, HHARI, that regulate its interaction with the ubiquitin-conjugating enzyme, UbcH7
AUTHOR: Ardley Helen C (Reprint); Tan Nancy G S; Rose Stephen A; Markham Alexander F; Robinson Philip A
AUTHOR ADDRESS: Molecular Medicine Unit, St. James's University Hospital, Level 6, Clinical Sciences Bldg., Leeds, LS9 7TF, UK**UK
JOURNAL: Journal of Biological Chemistry 276 (22): p19640-19647 June 1, 2001 2001
MEDIUM: print
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We recently reported the identification of a RING finger-containing protein, HHARI (human homologue of Drosophila ariadne), which binds to the human ubiquitin-conjugating enzyme UbcH7 in vitro. We now demonstrate that HHARI interacts and co-localizes with UbcH7 in mammalian cells, particularly in the perinuclear region. We have further defined a minimal interaction region of HHARI comprising residues 186-254, identified individual amino acid residues essential for the interaction, and determined that the distance between the RING1 finger and IBR (in between RING fingers) domains is critical to maintaining %%%binding%%%. We have also established that the RING1 finger of HHARI cannot be substituted for by the highly homologous RING finger domains of either of the ubiquitin-protein ligase components c-CBL or %%%Parkin%%%, despite their similarity in structure and their independent capabilities to bind UbcH7. Furthermore, mutation of the RING1 finger domain of HHARI from a RING-HC to a RING-H2 type abolishes interaction with UbcH7. These studies demonstrate that very subtle changes to the domains that regulate recognition between highly conserved components of the ubiquitin pathway can dramatically affect their ability to interact.

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DIALOG(R)File 5:Biosis Previews(R)

0013175665 BIOSIS NO.: 200100347504
An apparently sporadic case with %%%parkin%%% gene mutation in a Korean woman
AUTHOR: Jeon Beom S (Reprint); Kim Jong-Min; Lee Dong-Soo; Hattori Nobutaka ; Mizuno Yoshikuni
AUTHOR ADDRESS: Department of Neurology, Movement Disorder Division, Seoul National University Hospital, Chongno-Ku Yunkeun-Dong 28, Seoul, 110-744, South Korea**South Korea
JOURNAL: Archives of Neurology 58 (6): p988-989 June, 2001 2001
MEDIUM: print
ISSN: 0003-9942
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective: To report the clinical features and results of iodine I 123-2beta-carbomethoxy-3beta-(4-iodophenyl)-tropane (CIT) single photon emission computed tomography and molecular genetic analysis in a Korean woman with juvenile Parkinson disease with deletion in exon 4 of the %%%parkin%%% gene. Design: Case report with molecular genetic analysis. Patient and Results: The patient had bradykinesia, postural imbalance, and postural tremor since the age of 12 years. She developed wearing off early in the disease course. The (123I)-2beta-carbomethoxy-3beta-(4-iodophenyl)-tropane single photon emission computed tomography showed severe reduction of specific striatal CIT %%%binding%%%, comparable to that of Parkinson disease. The polymerase chain reaction products from the %%%parkin%%% gene showed homozygous exon 4 deletion. Conclusion: In this sporadic juvenile Parkinson disease case, severe nigrostriatal dopaminergic damage and homozygous exon 4 deletion in the %%%parkin%%% gene were demonstrated.

5/7/47

DIALOG(R)File 5:Biosis Previews(R)

0013046639 BIOSIS NO.: 200100218478
The dopaminergic system in autosomal recessive parkinsonism associated with mutations in the %%%parkin%%% gene measured by positron emission tomography
AUTHOR: Hilker R (Reprint); Kis B; Klein C; Lenz O; Strotmann T (Reprint); Ozelius L J; Vieregge P; Herholz K (Reprint); Pramstaller P P; Heiss W-D (Reprint)
AUTHOR ADDRESS: Klinik und Poliklinik fuer Neurologie, Universitaet zu Koeln, Koeln, Germany**Germany
JOURNAL: European Journal of Neurology 7 (Supplement 3): p113 November, 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 5th Congress of the European Federation of Neurological Societies Copenhagen, Denmark October 14-18, 2000; 20001014
SPONSOR: European Federation of Neurological Societies
ISSN: 1351-5101
DOCUMENT TYPE: Meeting; Meeting Abstract; Meeting Poster
RECORD TYPE: Citation
LANGUAGE: English

5/7/48
DIALOG(R)File 5:Biosis Previews(R)

0013025908 BIOSIS NO.: 200100197747
Proteins of neurodegenerative diseases scrapie (cellular prion, PrP), Alzheimer (amyloid precursor, APP), Parkinson (%%%parkin%%%, P) and Huntington (huntingtin, H) are related in canonical (Cu/Zn)-metalloregulator and RNA-%%%binding%%% (R3H) domains
AUTHOR: Wissler Josef H (Reprint); Logemann Enno
AUTHOR ADDRESS: ARCONS Applied Research Institute, D-61231, Bad Nauheim, Germany**Germany
JOURNAL: Biophysical Journal 80 (1 Part 2): p566a January, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 45th Annual Meeting of the Biophysical Society Boston, Massachusetts, USA February 17-21, 2001; 20010217
SPONSOR: Biophysical Society
ISSN: 0006-3495
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/7/49
DIALOG(R)File 5:Biosis Previews(R)

0013019232 BIOSIS NO.: 200100191071
Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the %%%parkin%%% gene
AUTHOR: Hilker Ruediger; Klein Christine; Ghaemi Mehran; Kis Bernhard; Strotmann Tim; Ozelius Laurie J; Lenz Olaf; Vieregge Peter; Herholz Karl; Heiss Wolf-Dieter (Reprint); Pramstaller Peter P
AUTHOR ADDRESS: Klinik und Poliklinik fuer Neurologie, Universitaet zu Koeln, Joseph-Stelzmann-Strasse 9, D-50924, Koeln, Germany**Germany
JOURNAL: Annals of Neurology 49 (3): p367-376 March, 2001 2001
MEDIUM: print
ISSN: 0364-5134
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A kindred from South Tyrol (northern Italy) with familial, adult-onset parkinsonism of pseudo-dominant inheritance and mutations in the %%%parkin%%% gene was recently described. To gain insight into basal ganglia dysfunction in this form of hereditary parkinsonism, positron

emission tomography (PET) with 18-fluorodopa (FDOPA) and 11C-raclopride (RAC) was performed in 5 affected family members and 5 asymptomatic relatives with proven compound heterozygous or heterozygous %%%parkin%%% mutations. Results were compared to findings in healthy control subjects and patients with typical sporadic, idiopathic Parkinson's disease. Similar to findings in the sporadic Parkinson's disease group, presynaptic striatal FDOPA storage was decreased in patients with compound heterozygous %%%parkin%%% mutations, with the most prominent reduction in the posterior part of the putamen. Along with the presynaptic lowered FDOPA uptake, we found a uniform reduction of the striatal 11C-raclopride %%%binding%%% index in all affected family members as compared to asymptomatic family members carrying a heterozygous %%%parkin%%% mutation, sporadic Parkinson's disease, and control subjects. Our PET data provide evidence that parkinsonism in this family is associated with presynaptic dopaminergic dysfunction similar to idiopathic Parkinson's disease pathophysiology, along with alterations at the postsynaptic D2 receptor level. In asymptomatic carriers of a single %%%parkin%%% mutation with an apparently normal allele, we found a mild but statistically significant decrease of mean FDOPA uptake compared to control subjects in all striatal regions. These data indicate a preclinical disease process in these subjects.

5/7/50
DIALOG(R)File 5:Biosis Previews(R)

0012904049 BIOSIS NO.: 200100075888
%%%Parkin%%% associates with the actin-%%%binding%%% protein filamin
AUTHOR: Choi P (Reprint); Passer B; Farrer M; D'Adamio L; Sparkman D; Lee J M; Wolozin B
AUTHOR ADDRESS: Loyola Univ School of Medicine, Maywood, IL, USA**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2): pAbstract No.-13.11 2000 2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000; 20001104
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mutations in the %%%Parkin%%% gene cause a familial variant of Parkinson's disease known as autosomal recessive juvenile Parkinsonism. Using both two-hybrid screening and immunoprecipitations from human brain, we have now shown that %%%Parkin%%% binds both actin and the actin-%%%binding%%% protein, filamin. Immunohistochemical studies of human brain show that %%%Parkin%%% is present in neurons and that %%%Parkin%%% accumulates in axonal spheroids and some Lewy bodies. The association of %%%Parkin%%% with filamin, but not with actin, is reduced in Parkinson's disease, which suggests that abnormalities in the regulation of the cytoskeleton by %%%Parkin%%% might play a general role in the pathophysiology of Parkinson's disease.

5/7/51
DIALOG(R)File 5:Biosis Previews(R)

0012711659 BIOSIS NO.: 200000429972
Iminoribitol transition state analogue inhibitors of protozoan nucleoside hydrolases
AUTHOR: Miles Robert W; Tyler Peter C; Evans Gary B; Furneaux Richard H; Parkin David W; Schramm Vern L (Reprint)
AUTHOR ADDRESS: Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY, 10461, USA**USA
JOURNAL: Biochemistry 38 (40): p13147-13154 Oct. 5, 1999 1999
MEDIUM: print
ISSN: 0006-2960
DOCUMENT TYPE: Article

RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Nucleoside N-ribohydrolases from protozoan parasites are targets for inhibitor design in these purine-auxotrophic organisms. Purine-specific and purine/pyrimidine-nonspecific nucleoside hydrolases have been reported. Iminoribitols that are 1-substituted with meta- and para-derivatized phenyl groups ((1S)-substituted 1,4-dideoxy-1,4-imino-D-ribitols) are powerful inhibitors for the nonspecific nucleoside N-ribohydrolases, but are weak inhibitiors for purine-specific isozymes (%%%Parkin%%%, D. W., Limberg, G., Tyler, P. C., Furneaux, R. H., Chen, X.-Y., and Schramm, V. L. (1997) Biochemisty 36, 3528-3534). %%%Binding%%% of these inhibitors to nonspecific nucleoside hydrolase occurs primarily via interaction with the iminoribitol, a ribooxocarbenium ion analogue of the transition state. Weaker interactions arise from hydrophobic interactions between the phenyl group and the purine/pyrimidine site. In contrast, the purine-specific enzymes obtain equal catalytic potential from leaving group activation and ribooxocarbenium ion formation. Knowledge of the reaction mechanisms and transition states for these enzymes has guided the design of isozyme-specific transition state analogue inhibitors. New synthetic efforts have produced novel inhibitors that incorporate features of the leaving group hydrogen-bonding sites while retaining the iminoribitol group. These compounds provide the first transition state analogue inhibitors for purine-specific nucleoside hydrolase. The most inhibitory 1-substituted iminoribitol heterocycle is a sub-nanomolar inhibitor for the purine-specific nucleoside hydrolase from Trypanosoma brucei brucei. Novel nanomolar inhibitors are also described for the nonspecific nucleoside hydrolase from Crithidia fasciculata. The compounds reported here are the most powerful iminoribitol inhibitors yet described for the nucleoside hydrolases.

5/7/52
DIALOG(R)File 5:Biosis Previews(R)

0012330897 BIOSIS NO.: 200000049210
Prediction of inhibitor %%%binding%%% free energies by quantum neural networks. Nucleoside analogues %%%binding%%% to trypanosomal nucleoside hydrolase
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JOURNAL: Biochemistry 38 (49): p16076-16083 Dec. 7, 1999 1999
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ABSTRACT: A computational method has been developed to predict inhibitor %%%binding%%% energy for untested inhibitor molecules. A neural network is trained from the electrostatic potential surfaces of known inhibitors and their %%%binding%%% energies. The algorithm is then able to predict, with high accuracy, the %%%binding%%% energy of unknown inhibitors. IU-nucleoside hydrolase from Crithidia fasciculata and the inhibitor molecules described previously (Miles, R. W. Tyler, P. C. Evans, G. Furneaux R. H., %%%Parkin%%%, D. W., and Schramm, V. L. (1999) Biochemistry 38, xxxx-xxxx) are used as the test system. Discrete points on the molecular electrostatic potential surface of inhibitor molecules are input to neural networks to identify the quantum mechanical features that contribute to %%%binding%%%. Feed-forward neural networks with back-propagation of error are trained to recognize the quantum mechanical electrostatic potential and geometry at the entire van der Waals surface of a group of training molecules and to predict the strength of interactions between the enzyme and novel inhibitors. The %%%binding%%% energies of unknown inhibitors were predicted, followed by experimental determination of Ki values. Predictions of Ki values using this theory are compared to other methods and are more robust in estimating

inhibitory strength. The average deviation in estimating Ki values for 18 unknown inhibitor molecules, with 21 training molecules, is a factor of 5 X Ki over a range of 660 000 in Ki values for all molecules. The a posteriori accuracy of the predictions suggests the method will be effective as a guide for experimental inhibitor design.

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DIALOG(R)File 5:Biosis Previews(R)

0010406146 BIOSIS NO.: 199699040206
Three-dimensional structure of the inosine-uridine nucleoside N-ribohydrolase from Crithidia fasciculata
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JOURNAL: Biochemistry 35 (19): p5971-5981 1996 1996
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DOCUMENT TYPE: Article
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ABSTRACT: Protozoan parasites rely on the host for purines since they lack a de novo synthetic pathway. Crithidia fasciculata salvages exogenous inosine primarily through hydrolysis of the N-ribosidic bond using several nucleoside hydrolases. The most abundant nucleoside hydrolase is relatively nonspecific but prefers inosine and uridine as substrates. Here we report the three-dimensional structure of the inosine-uridine nucleoside hydrolase (IU-NH) from C. fasciculata determined by X-ray crystallography at a nominal resolution of 2.5 ANG . The enzyme has an open (alpha,beta) structure which differs from the classical dinucleotide %%%binding%%% fold. IU-nucleoside hydrolase is composed of a mixed eight-stranded beta sheet surrounded by six alpha helices and a small C-terminal lobe composed of four alpha helices. Two short antiparallel beta strands are involved in intermolecular contacts. The catalytic pocket is located at the C-terminal end of beta strands beta-1 and beta-4. Four aspartate residues are located at the bottom of the cavity in a geometry which suggests interaction with the ribose moiety of the nucleoside. These groups could provide the catalytically important interactions to the ribosyl hydroxyls and the stabilizing anion for the oxycarbonium-like transition state. Histidine 241, located on the side of the active site cavity, is the proposed proton donor which facilitates purine base departure (Gopaul, D. N., Meyer, S. L., Degano, M., Sacchettini, J. C., and Schramm, V. L. (1996) Biochemistry 35, 5963-5970). The substrate %%%binding%%% site is unlike that from purine nucleoside phosphorylase, phosphoribosyltransferase, or uracil DNA glycosylase and thus represents a novel architecture for general acid-base catalysis. This detailed knowledge of the architecture of the active site, together with the previous transition state analysis (Horenstein, B. A., %%%Parkin%%%, D. W., Estupinan, B., and Schramm, V. L. (1991) Biochemistry 30, 10788-10795), allows analysis of the interactions leading to catalysis and an explanation for the tight-%%%binding%%% inhibitors of the enzyme (Schramm, V. L., Horenstein, B. A., and Kline, P. C. (1994) J. Biol. Chem. 269, 18259-18262).

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DIALOG(R)File 5:Biosis Previews(R)

0010163407 BIOSIS NO.: 199698631240
%%%Binding%%% modes for substrate and a proposed transition-state analogue of protozoan nucleoside hydrolase
AUTHOR: Parkin David W; Schramm Vern L (Reprint)
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JOURNAL: Biochemistry 34 (42): p13961-13966 1995 1995
ISSN: 0006-2960
DOCUMENT TYPE: Article

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LANGUAGE: English

ABSTRACT: The transition-state structure for inosine-uridine nucleoside hydrolase (IU-nucleoside hydrolase) from Crithidia fasciculata is characterized by oxycarbonium character in the ribosyl and weak bonds to the departing hypoxanthine and incipient water nucleophile (Horenstein, B. A., %%%Parkin%%%, D. W., Estupinan, B., and Schramm, V. L. (1991) Biochemistry 30, 10788-107951. Inhibitors designed to resemble the transition state are slow-onset, tight-%%%binding%%% inhibitors with observed K-m/K-i values up to 2 times 10-5 (Schramm, V. L., Horenstein, B. H., and Kline, P. C. (1994) J. Biol. Chem. 269, 18259-18262). Although slow-onset, tight %%%binding%%% is consistent with transition-state stabilization, more direct evidence can be obtained by comparing the groups which interact with the substrate to provide %%%binding%%% and catalysis with those which interact with the putative transition-state inhibitor. The K-m value for inosine %%%binding%%% to IU-nucleoside hydrolase is independent of pH over the range 5.6-10.5. Dependencies of V-max and V-max/K-m on pH result in pH optima near 8.0. A single group with pK of 9.1 must be protonated for catalytic activity, and protonation of a second group with a pK of 7.1 results in loss of activity. 1-(S)-Phenyl-1,4-dideoxy-1,4-imino-D-ribitol (phenyliminoribitol) binds with an equilibrium K-d of 30 nM and has been proposed to be a transition-state inhibitor. The pH dependence for the competitive inhibition by phenyliminoribitol resembles the V-max profile with the protonation of a single group, pK 7.5, required for inhibitor %%%binding%%% and the protonation of a subsequent group, pK 6.6, causing loss of %%%binding%%%. It has been proposed that the positive charge of protonated inhibitor (pK 6.5) is a recognition feature for %%%binding%%% as a transition-state inhibitor. However, the pH analysis indicates that the neutral inhibitor is the preferred species for %%%binding%%% the active form of the enzyme. The slow-onset phase of phenyliminoribitol %%%binding%%% disappears at low pH, suggesting that a time-dependent protonation of the bound complex could be responsible for the slow-onset phase of inhibition.

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0009215985 BIOSIS NO.: 199497237270
Amidrazone analogues of D-ribofuranose as transition-state inhibitors of nucleoside hydrolase
AUTHOR: Boutellier Markus; Horenstein Benjamin A; Semenyaka Alexi; Schramm Vern L (Reprint); Ganem Bruce
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JOURNAL: Biochemistry 33 (13): p3994-4000 1994 1994
ISSN: 0006-2960
DOCUMENT TYPE: Article
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LANGUAGE: English

ABSTRACT: The transition state of inosine during hydrolysis by nucleoside hydrolase has been characterized by kinetic isotope effects, bond-energy/bond-order vibrational analysis, and molecular electrostatic potential surface calculations (Horenstein, B. A., %%%Parkin%%%, D. W., Estupinan, B., and Schramm, V. L. (1991) Biochemistry 30, 10788-10795; Horenstein, B. A., and Schramm, V. L. (1993) Biochemistry 32, 7089-7097). The heterocyclic base is protonated and the anomeric carbon of the ribofuranosyl ring is flattened to form a transition-state with extensive oxocarbenium ion character. With their delocalized charge and flattened structures, amidrazone analogues of D-ribofuranose provide both geometric and electronic mimics of the ribosyl group at the transition-state of nucleoside hydrolase. A family of riboamidrazones was synthesized with H, phenyl, and p-nitrophenyl N-substituents. The analogues were competitive inhibitors with respect to inosine and gave K-i values of 10-5, 2 times 10-7, and 1 times 10-8M, respectively. (p-Nitrophenyl)riboamidrazone exhibited slow-onset, tight-%%%binding%%% inhibition, with an overall dissociation constant of 2 times 10-9 M. The %%%binding%%% is reversible

with an off-rate of 3 times 10-3 s-1. Tight %%%binding%%% can be attributed to the close spatial match between the molecular geometry of (p-nitrophenyl)riboamidrazone and the transition-state stabilized by nucleoside hydrolase. The favorable %%%binding%%% interactions of the (p-nitrophenyl)riboamidrazone include oxocarbenium ion mimicry, isosteric ribosyl hydroxyls, and hydrophobic and H-bonding interactions at the nitrophenyl group. Analysis of the conformational space available to the (p-nitrophenyl)riboamidrazone indicates that the geometry that approximates the enzyme-stabilized transition state is 7-14 kcal/mol unfavorable relative to the global conformational minimum for free inhibitor. The apparent overall K-d of 2 nM represents only a fraction of the intrinsic energy available for transition-state interactions with nucleoside hydrolase. When corrected for the energy of distortion required to achieve the transition-state conformation, (p-nitrophenyl)riboamidrazone binds with an affinity near that expected for an ideal transition-state analogue.

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DIALOG(R)File 5:Biosis Previews(R)

0008970921 BIOSIS NO.: 199396135337
Correlation of the molecular electrostatic potential surface of an enzymatic transition state with novel transition-state inhibitors
AUTHOR: Horenstein Benjamin A; Schramm Vern L (Reprint)
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JOURNAL: Biochemistry 32 (38): p9917-9925 1993
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The transition state stabilized by nucleoside hydrolase from Crithidia fasciculata is characterized by nearly complete glycosidic bond cleavage and oxycarbonium character in the ribosyl group (Horenstein, B. A., %%%Parkin%%%, D. W., Estupinan, B., and Schramm, V. L. (1991) Biochemistry 30, 10788-10795). The electrostatic potential surface of the transition state provides detailed information which should be useful in the design of transition-state analogues (Horenstein, B. A., and Schramm, V. L. (1993) Biochemistry 32, 7089-7097). The electrostatic potential surface of inosine at the transition state contains a distributed positive charge resulting from the oxycarbonium ion character of the ribosyl ring. The ribosyl ring pucker is 3'-exo as a result of the near sp-2 hybridization at C1' of the ribose ring. A series of transition-state analogues have been synthesized which incorporate single or combined features of the transition state. Each feature of the transition state was analyzed for its contribution to %%%binding%%% energy. Kinetic inhibition constants correlate with the similarity of the inhibitor to the experimentally determined transition-state structure. Dissociation constants for the substrate and products of the reaction of inosine, hypoxanthine, and ribose are 380, 6200, and 700 mu-M, respectively. A transition-state analogue was synthesized which contains the required hydroxyl groups of the ribose ring, the positive charge feature of the oxycarbonium ion, and a hydrophobic mimic of the purine ring. The inhibitor 1(S)-phenyl-1,4-dideoxy-1,4-iminoribitol acts as a competitive inhibitor with respect to inosine with a dissociation constant of 0.17 mu-M. In addition, the inhibitor exhibits slow-onset inhibition which provides a final equilibrium dissociation constant of approximately 0.03 mu-M. The affinity of inhibitor %%%binding%%% correlates to the match between the electrostatic potential surfaces of the inhibitors and the transition states but less well to the geometric similarity. The results establish that an enzymatic transition state characterized by a family of kinetic isotope effects, bond vibrational analysis, and molecular electrostatic potentials facilitates the design of transition-state inhibitors.

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DIALOG(R)File 5:Biosis Previews(R)

0007697449 BIOSIS NO.: 199191080340
THE INTEGRITY OF THE STEM STRUCTURE OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 TAT-RESPONSIVE SEQUENCE RNA IS REQUIRED FOR INTERACTION WITH THE INTERFERON-INDUCED 68000-M-R PROTEIN KINASE
AUTHOR: ROY S (Reprint); AGY M; HOVANESSIAN A G; SONENBERG N; KATZE M G
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JOURNAL: Journal of Virology 65 (2): p632-640 1991
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A number of eucaryotic viruses have devised strategies to minimize the deleterious effects on protein synthesis caused by activation of the interferon-induced, double-stranded-RNA-activated protein kinase, P68. In a recent report, we described the down regulation of the P68 protein kinase in cells infected by human immunodeficiency virus type 1 (HIV-1) (S. Roy, M G. Katze, N. T. %%%Parkin%%%, I. Edery, A. G. Hovanessian, and N. Sonenberg, Science 247:1216-1219, 1990). We now present evidence that such a decrease in amounts of P68 could be essential for HIV-1 replication because of the presence of the Tat-responsive sequence (TAR sequence) present in the 5' untranslated region of HIV-1 mRNAs, which activates the P68 kinase. We found that poly(A)+ mRNAs prepared from HIV-1-infected cells efficiently activated the protein kinase as did mRNAs from stably transformed cell lines constitutively expressing the TAR region. Furthermore, we found that TAR-containing RNAs complexed with purified P68 protein kinase in vitro by two independent assays and could be cross-linked to P68 kinase present in a HeLa cell extract. Experiments using in vitro-synthesized wild-type and mutant TAR RNAs revealed that both the efficient %%%binding%%% to and the activation of P68 kinase were dependent on the TAR RNA stem structure. The TAR-P68 complex could be competed out by a synthetic RNA that bound to and activated the protein kinase but not by a synthetic RNA that bound with low affinity and did not activate P68. The possible biological consequences of a P68-TAR interaction that may include the switch from latent to active virus replication are discussed.

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DIALOG(R)File 5:Biosis Previews(R)

0014365745 BIOSIS NO.: 200300324041
The %%%p38%%% subunit of the aminoacyl-tRNA synthetase complex is a Parkin substrate: Linking protein biosynthesis and neurodegeneration.
AUTHOR: Corti Olga; %%%Hampe Cornelia%%%; Koutnikova Hana; Darios Frederic; Jacquier Sandrine; Prigent Annick; Robinson Jean-Charles; %%%Pradier%%% %%% Laurent%%%; Ruberg Merle; Mirande Marc; Hirsch Etienne; %%%Rooney%%% %%% Thomas%%%; %%%Fournier Alain%%%; %%%Brice Alexis%%% (Reprint
AUTHOR ADDRESS: INSERM U289, Hopital de la Salpetriere, 47 Boulevard de l'Hopital, Batiment Pharmacie, 75651, Paris Cedex 13, France**France
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JOURNAL: Human Molecular Genetics 12 (12): p1427-1437 15 June, 2003 2003
MEDIUM: print
ISSN: 0964-6906 _(ISSN print)
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LANGUAGE: English

ABSTRACT: Parkinson's disease (PD) is a severe neurological disorder, characterized by the progressive degeneration of the dopaminergic nigrostriatal pathway and the presence of Lewy bodies (LBs). The discovery of genes responsible for familial forms of the disease has provided insights into its pathogenesis. Mutations in the parkin gene, which encodes an E3 ubiquitin-protein ligase involved in the ubiquitylation and proteasomal degradation of specific protein substrates, have been found in nearly 50% of patients with

autosomal-recessive early-onset parkinsonism. The abnormal accumulation of substrates due to loss of Parkin function may be the cause of neurodegeneration in parkin-related parkinsonism. Here, we demonstrate that Parkin interacts with, ubiquitylates and promotes the degradation of %%%p38%%%, a key structural component of the mammalian aminoacyl-tRNA synthetase complex. We found that the ubiquitylation of %%%p38%%% is abrogated by truncated variants of Parkin lacking essential functional domains, but not by the pathogenic Lys161Asn point mutant. Expression of %%%p38%%% in COS7 cells resulted in the formation of aggresome-like inclusions in which Parkin was systematically sequestered. In the human dopaminergic neuroblastoma-derived SH-SY5Y cell line, Parkin promoted the formation of ubiquitylated %%%p38%%%-positive inclusions. Moreover, the overexpression of %%%p38%%% in SH-SY5Y cells caused significant cell death against which Parkin provided protection. Analysis of %%%p38%%% expression in the human adult midbrain revealed strong immunoreactivity in normal dopaminergic neurons and the labeling of LBs in idiopathic PD. This suggests that %%%p38%%% plays a role in the pathogenesis of PD, opening the way for a detailed examination of its potential non-canonical role in neurodegeneration.

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DIALOG(R)File 5:Biosis Previews(R)

0013656045 BIOSIS NO.: 200200249556
Extracellular signal-regulated kinase plays an essential role in endothelin-1-induced homotypic adhesion of human neutrophil granulocytes
AUTHOR: Jozsef Levente; Khreiss Tarek; %%%Fournier Alain%%%; Chan John S D; Filep Janos G (Reprint
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JOURNAL: British Journal of Pharmacology 135 (5): p1167-1174 March, 2002
2002
MEDIUM: print
ISSN: 0007-1188
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RECORD TYPE: Abstract
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ABSTRACT: 1 Endothelin-1 (ET-1) stimulates integrin-dependent adhesion of neutrophil granulocytes to endothelial cells, one of the early key events in acute inflammation. However, the signalling pathway(s) of ET-1-stimulated neutrophil adhesive responses has not been elucidated. Previous studies indicated that extracellular signal-regulated kinase (ERK) activation could mediate rapid responses of neutrophil granulocytes to various stimuli. In this study, we investigated the role of ERK signalling in human neutrophil granulocytes challenged with ET-1. 2 ET-1 rapidly down-regulated the expression of L-selectin and up-regulated the expression of CD11b/CD18 on the neutrophil surface. Concomitantly, ET-1 induced homotypic adhesion (aggregation) of neutrophils, that was blocked by a monoclonal antibody to CD18. 3 ET-1, through ETA receptors, evoked activation of Ras and subsequent phosphorylation of Raf-1, mitogen-activated protein kinase kinase (MAPK/ERK kinase) and ERK 1/2. ERK activation by ET-1 was rapid, concordant with the kinetics of ET-1-stimulated neutrophil aggregation. 4 Neutrophil responses to ET-1 were markedly attenuated by the MAPK/ERK kinase inhibitor PD98059, whereas inhibitors of %%%p38%%% MAPK, tyrosine kinases and phosphatidylinositol 3-kinase had no detectable effects. We have observed a tight correlation between neutrophil ERK activation and homotypic adhesion. 5 These data indicate an essential role for ERK in mediating ET-1-stimulated adhesive responses of human neutrophil granulocytes.

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$6.40 TELNET

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